Pravachol—Cont.

Table 9: Adverse Events in ≥1 Percent of Patients Treated with Pravastatin 40 mg in Long-Term Placebo-Controlled Trials

Body System/Event	Pravastatin (N=10,764) % of patients	Placebo (N=10,719) % of patients
Cardiovascular		
Angina Pectoris	3.1	3.4
Dermatologic		
Rash	2.1	2.2
Gastrointestinal		
Dyspepsia/Heartburn	3.5	3.7
Abdominal Pain	2.4	2.5
Nausea/Vomiting	1.6	1.6
Flatulence	1.2	1.1
Constipation	1.2	1.3
General		
Fatigue	3.4	3.3
Chest Pain	2.6	2.6
Musculoskeletal		
Musculoskeletal Pain (includes arthralgia)	6.0	5.8
Muscle Cramp	2.0	1.8
Myalgia	1.4	1.4
Nervous System		
Dizziness	2.2	2.1
Headache	1.9	1.8
Sleep Disturbance	1.0	0.9
Depression	1.0	1.0
Anxiety/Nervousness	1.0	1.2
Renal/Genitourinary		
Urinary Abnormality (includes dysuria, frequency, nocturia)	1.0	0.8
Respiratory		
Dyspnea	1.6	1.6
Upper Respiratory Infection	1.3	1.3
Cough	1.0	1.0
Special Senses		
Vision Disturbance (includes blurred vision, diplopia)	1.6	1.3

Events of probable, possible, or uncertain relationship to study drug that occurred in <1.0% of pravastatin-treated patients in the long-term trials included the following; frequencies were similar in placebo-treated patients:
Dermatologic: pruritus, dermatitis, dryness of skin, scalp hair abnormality (including alopecia), urticaria.
Endocrine/Metabolic: sexual dysfunction, libido change.
Gastrointestinal: decreased appetite.
General: fever, flushing.
Immunologic: allergy, edema head/neck.
Musculoskeletal: muscle weakness.
Nervous System: paresthesia, vertigo, insomnia, memory impairment, tremor, neuropathy (including peripheral neuropathy).
Special Senses: lens opacity, taste disturbance.

Postmarketing Experience

In addition to the events reported above, as with other drugs in this class, the following events have been reported rarely during postmarketing experience with PRAVACHOL (pravastatin sodium), regardless of causality assessment:
Musculoskeletal: myopathy, rhabdomyolysis.
Nervous System: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), peripheral nerve palsy.
Hypersensitivity: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, asthenia, photosensitivity, chills, malaise, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.
Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, cirrhosis, fulminant hepatic necrosis, hepatoma.
Dermatologic: A variety of skin changes (e.g., nodules, discoloration, dryness of mucous membranes, changes to hair/nails).
Reproductive: gynecomastia.
Laboratory Abnormalities: LFT abnormalities, thyroid function abnormalities.

Laboratory Test Abnormalities

Increases in serum transaminase (ALT, AST) values and CPK have been observed (see **WARNINGS**).
Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with HMG-CoA reductase inhibitors.

Concomitant Therapy

Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is **not** associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See **WARNINGS: Skeletal Muscle** and **PRECAUTIONS: Drug Interactions.**)

Pediatric Patients

In a two year, double-blind, placebo-controlled study involving 100 boys and 114 girls with HeFH, the safety and tolerability profile of pravastatin was generally similar to that of placebo. (See **CLINICAL PHARMACOLOGY, Pediatric Clinical Study** and **PRECAUTIONS, Pediatric Use.**)

OVERDOSAGE

To date, there has been limited experience with overdosage of pravastatin. If an overdose occurs, it should be treated symptomatically with laboratory monitoring and supportive measures should be instituted as required. (See **WARNINGS.**)

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving PRAVACHOL (pravastatin sodium) and should continue on this diet during treatment with PRAVACHOL (see NCEP Treatment Guidelines for details on dietary therapy).
PRAVACHOL can be administered orally as a single dose at any time of the day, with or without food. Since the maximal effect of a given dose is seen within 4 weeks, periodic lipid determinations should be performed at this time and dosage adjusted according to the patient's response to therapy and established treatment guidelines.

Adult Patients

The recommended starting dose is 40 mg once daily. If a daily dose of 40 mg does not achieve desired cholesterol levels, 80 mg once daily is recommended. In patients with a history of significant renal or hepatic dysfunction, a starting dose of 10 mg daily is recommended.

Pediatric Patients

Children (Ages 8 to 13 Years, Inclusive)

The recommended dose is 20 mg once daily in children 8 to 13 years of age. Doses greater than 20 mg have not been studied in this patient population.

Adolescents (Ages 14 to 18 Years)

The recommended starting dose is 40 mg once daily in adolescents 14 to 18 years of age. Doses greater than 40 mg have not been studied in this patient population.
Children and adolescents treated with pravastatin should be reevaluated in adulthood and appropriate changes made to their cholesterol-lowering regimen to achieve adult goals for LDL-C (see **INDICATIONS AND USAGE, Hyperlipidemia, NCEP Treatment Guidelines**).
In patients taking immunosuppressive drugs such as cyclosporine (see **WARNINGS: Skeletal Muscle**) concomitantly with pravastatin, therapy should begin with 10 mg of pravastatin once-a-day at bedtime and titration to higher doses should be done with caution. Most patients treated with this combination received a maximum pravastatin dose of 20 mg/day.

Concomitant Therapy

The lipid-lowering effects of PRAVACHOL on total and LDL cholesterol are enhanced when combined with a bile-acid-binding resin. When administering a bile-acid-binding resin (e.g., cholestyramine, colestipol) and pravastatin, PRAVACHOL should be given either 1 hour or more before or at least 4 hours following the resin. (See also **ADVERSE REACTIONS: Concomitant Therapy.**)

HOW SUPPLIED

PRAVACHOL® (pravastatin sodium) Tablets are supplied as:
10 mg tablets: Pink to peach, rounded, rectangular-shaped, biconvex with a "P" embossed on one side and "PRAVACHOL 10" engraved on the opposite side. They are supplied in bottles of 90 (NDC 0003-5154-05). Bottles contain a desiccant canister.
20 mg tablets: Yellow, rounded, rectangular-shaped, biconvex with a "P" embossed on one side and "PRAVACHOL 20" engraved on the opposite side. They are supplied in bottles of 90 (NDC 0003-5178-05), bottles of 1000 (NDC 0003-5178-75), and hospital unit-dose packages of 100 tablets (NDC 0003-5178-06). Bottles contain a desiccant canister.
40 mg tablets: Green, rounded, rectangular-shaped, biconvex with a "P" embossed on one side and "PRAVACHOL 40" engraved on the opposite side. They are supplied in bottles of 90 (NDC 0003-5194-10) and hospital unit-dose packages of 100 tablets (NDC 0003-5194-33). Bottles contain a desiccant canister.
80 mg tablets: Yellow, oval-shaped, tablet with "BMS" on one side and "80" on the other side. They are supplied in bottles of 90 (NDC 0003-5195-10), bottles of 500 (NDC 0003-5195-12), and hospital unit-dose packages of 100 tablets (NDC 0003-5195-33). Bottles contain a desiccant canister.

STORAGE

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Keep tightly closed (protect from moisture). Protect from light.

REFERENCES

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US Patent Nos.: 4,346,227; 5,030,447; 5,180,589; 5,622,985

Bristol-Myers Squibb Company
Princeton, NJ 08543 U.S.A.

D3-B0001-12-04 5154DIM-24
Revised December 2004

Shown in Product Identification Guide, page 309

REYATAZ®

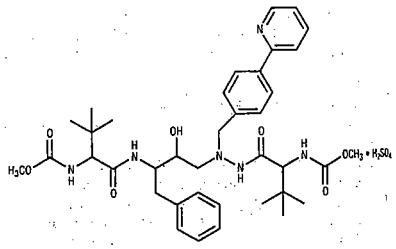
℞

[rā'ă-tăz]
(atazanavir sulfate) Capsules
℞ ONLY

(Patient Information Leaflet Included)

DESCRIPTION

REYATAZ® (atazanavir sulfate) is an azapeptide inhibitor of HIV-1 protease.
The chemical name for atazanavir sulfate is (3*S*,8*S*,9*S*,12*S*)-3,12-Bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-[[4-(2-pyridinyl)phenyl]methyl]-2,5,6,10,13-pentaazatetradecanedioic acid dimethyl ester, sulfate (1:1). Its molecular formula is $C_{38}H_{52}N_6O_7 \cdot H_2SO_4$, which corresponds to a molecular weight of 802.9 (sulfuric acid salt). The free base molecular weight is 704.9. Atazanavir sulfate has the following structural formula:



Atazanavir sulfate is a white to pale yellow crystalline powder. It is slightly soluble in water (4-5 mg/mL, free base equivalent) with the pH of a saturated solution in water being about 1.9 at 24 ± 3° C.
REYATAZ Capsules are available for oral administration in strengths containing the equivalent of 100 mg, 150 mg, or 200 mg of atazanavir as atazanavir sulfate and the following inactive ingredients: crospovidone, lactose monohydrate, and magnesium stearate. The capsule shells contain the following inactive ingredients: gelatin, FD&C Blue #2, and titanium dioxide. The capsules are printed with ink containing shellac, titanium dioxide, FD&C Blue #2, isopropyl alcohol, ammonium hydroxide, propylene glycol, n-butyl alcohol, simethicone, and dehydrated alcohol.

CLINICAL PHARMACOLOGY

Microbiology

Mechanism of Action

Atazanavir (ATV) is an azapeptide HIV-1 protease inhibitor (PI). The compound selectively inhibits the virus-specific processing of viral Gag and Gag-Pol polyproteins in HIV-1 infected cells, thus preventing formation of mature virions.

Antiviral Activity In Vitro

Atazanavir exhibits anti-HIV-1 activity with a mean 50% inhibitory concentration (IC_{50}) in the absence of human serum of 2 to 5 nM against a variety of laboratory and clinical HIV-1 isolates grown in peripheral blood mononuclear cells, macrophages, CEM-SS cells, and MT-2 cells. Two-drug combination studies with ATV showed additive to antago-

nistic antiviral activity
NNRTIs (delavirdine, ef
tive antiviral activity *in*
dinavir, lopinavir, nelfi
NRTIs (didanosine, emt
tenofovir, zalcitabine, an
hibitor enfuvirtide, and
ment of viral hepatitis,
hanced cytotoxicity.
Resistance
In vitro: HIV-1 isolate
ATV have been selected
treated with ATV or ata
isolates that were 93-
three different viral s
months. The mutations
uted to ATV resistance
and M46I. Changes w
cleavage sites followin
ruses containing the I5
and displayed increase
(amprenavir, indinavir,
saquinavir). The I50L
tive resistance to ATV a
not appear to be cross-
Clinical Studies of Tr
tant clinical isolates fr
perienced virologic fail
ter an average of 50
combination with an
patients, viral isolate
showed phenotypic res
susceptibility to other
nelfinavir, ritonavir, a
clinical data available
mutation on the effica
Clinical Studies of T
contrast, from studie
treated with ATV or A
from patients who ex
mutations that were
PIs and displayed dec
The most common pr
ral isolates of patie
300 mg once daily a
with tenofovir and
E35D/G, M46I/L, I50
V82A/T/L, I85V, and I
veloped on ATV/RTV
I84V, N88S/D/T, and I
tient isolates. General
were present in the I
resistance developed
sistance to other PIs
the I50L mutation.
Cross-Resistance
Cross-resistance amc
phenotypic and genot
ATV clinical trials of
isolates cross-resistar
to ATV. Greater thar
that included I84V o
than 60% of isolates
I54V, M46I/L, or a ch
38% of isolates conta
other changes were
ATV were also cross-
isolates resistant
ritonavir, and saquin
In treatment-experie
lates that developed
PI-resistance-associ
resistant to other PI
Genotypic and/or ph
aid in determining
ATV/RTV therapy.
sponse at 48 weeks
PI-resistance-associ
HIV-1 isolates from
ceiving ATV/RTV on
daily in Study AI42
Overall, both the nu
affected response ra
In the ATV/RTV gr
when 3 or more bas
at position 36, 71,
patients with 1–2 P
tations.

Table 1: HIV RNA F Baseline P Patients ir

Number and Type Baseline PI Mutations*
3 or more primary mutations includin
D30N
M36I/V
M46I/L/T
I54V/L/T/M/A

Thrombin/Thrombin-JMI—Cont.

WARNING

The use of topical bovine thrombin preparations has occasionally been associated with abnormalities in hemostasis ranging from asymptomatic alterations in laboratory determinations, such as prothrombin time (PT) and partial thromboplastin time (PTT), to severe bleeding or thrombosis which rarely have been fatal. These hemostatic effects appear to be related to the formation of antibodies against bovine thrombin and/or factor V which in some cases may cross react with human factor V, potentially resulting in factor V deficency. Repeated clinical applications of topical bovine thrombin increase the likelihood that antibodies against thrombin and/or factor V may be formed. Consultation with an expert in coagulation disorders is recommended if a patient exhibits abnormal coagulation laboratory values, abnormal bleeding, or abnormal thrombosis following the use of topical thrombin. Any interventions should consider the immunologic basis of this condition. Patients with antibodies to bovine thrombin preparations should not be re-exposed to these products.

Because of its action in the clotting mechanism, THROMBIN-JMI® must not be injected or otherwise allowed to enter large blood vessels. Extensive intravascular clotting and even death may result.

PRECAUTIONS

General—Consult the Absorbable Gelatin Sponge, USP labeling for complete information for use prior to utilizing the thrombin saturated sponge procedure.
Pregnancy—Category C – Animal reproduction studies have not been conducted with THROMBIN-JMI®. It is also not known whether THROMBIN-JMI® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. THROMBIN-JMI® should be given to a pregnant woman only if clearly indicated.
Pediatric Use—Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Allergic reactions may be encountered in persons known to be sensitive to bovine materials. Inhibitory antibodies which interfere with hemostasis may develop in a small percentage of patients. See **Warning**.

DOSAGE AND ADMINISTRATION

Solutions of Thrombin, Topical (Bovine Origin), USP, THROMBIN-JMI® may be reconstituted with sterile isotonic saline at a recommended concentration of 1,000 to 2,000 International Units/mL. Where bleeding is profuse, as from abraded surfaces of liver or spleen, concentrations of 1,000 International Units per mL may be required. For general use in plastic surgery, dental extractions, skin grafting, etc. solutions containing approximately 100 International Units/mL are frequently used. Intermediate strengths to suit the needs of the case may be prepared by diluting the contents of the THROMBIN-JMI® container with an appropriate volume of sterile isotonic saline. In many situations, it may be advantageous to use THROMBIN-JMI® in a dry form on oozing surfaces. THROMBIN-JMI® may also be used with FloSeal™ NT according to the directions for use in the FloSeal™ NT package insert.
In instances where a concentration of approximately 1,000 units/mL is desired, the contents of the vial of sterile isotonic saline diluent may be transferred into the THROMBIN-JMI® container with a sterile syringe or sterile transfer needle. If the transfer needle is used for reconstitution, transfer the diluent in the following manner.
1. Remove the plastic cap off of the diluent vial.
2. Twist the clear plastic cover on the transfer needle and remove.
3. Insert the exposed needle into the diaphragm of the diluent vial.
4. Flip the plastic cover up on the THROMBIN-JMI® container. DO NOT REMOVE THE ALUMINUM SEAL.
5. Remove the pink plastic cap from the transfer needle exposing the needle.
6. Invert the vial of diluent and insert the exposed needle into the diaphragm of the THROMBIN-JMI® container.

THROMBIN-JMI® SPRAY KIT
Each spray kit contains one vial of THROMBIN-JMI®, one vial of diluent and one spray pump and actuator.
1. Remove the outer lid by pulling up at the indicated edge. The inner tray is sterile and suitable for introduction into any operating field.
2. Remove the cover on inner tray to expose sterile contents.
3. Reconstitute the THROMBIN-JMI® to desired potency by introducing sterile isotonic saline with a sterile syringe or a sterile transfer needle. If the transfer needle is used, follow the previously described procedure.
4. When the THROMBIN-JMI® is completely dissolved, open vial by flipping up metal and tearing counterclockwise.
5. Remove the rubber diaphragm from vial. Remove pump with protective cap from tray and snap onto vial. Remove protective cap and attach actuator.
6. To spray, hold vial upright or at a slight angle. Several strokes of the pump will be required to expel the solution.
7. Discard unused contents and pump: DO NOT TRANSFER SPRAY PUMP TO ANOTHER VIAL.

THROMBIN-JMI® SYRINGE SPRAY KIT
Each syringe kit contains one vial of THROMBIN-JMI®, one vial of diluent and one spray tip and syringe.
1. Remove the outer lid by pulling up at the indicated edge. The inner tray is sterile and suitable for introduction into any operating field.
2. Remove the cover on the inner tray to expose sterile contents.
3. Using the sterile syringe equipped with a needle, draw the desired amount of saline diluent from the vial into the syringe.
4. Inject the saline diluent into the THROMBIN-JMI® thrombin vial from the syringe to reconstitute the THROMBIN-JMI® thrombin powder.
5. When the THROMBIN-JMI® powder is completely dissolved, draw the THROMBIN-JMI® Thrombin solution into the syringe.
6. Replace the needle guard.
7. Turn needle guard counterclockwise and remove and discard the needle.
8. Affix spray tip by pushing down and turning clockwise until the spray tip locks in place.
9. To spray, depress the syringe plunger in a normal fashion to dispense the THROMBIN-JMI® Thrombin solution through the tip in a fine spray.
10. Discard unused contents and syringe.

CAUTION: Solutions should be used promptly upon removal from the container. However, the solution may be refrigerated at 2-8°C for up to three hours.
The following techniques are suggested for the topical application of THROMBIN-JMI®.
1. The recipient surface should be sponged (not wiped) free of blood before THROMBIN-JMI® is applied.
2. A spray may be used or the surface may be flooded using a sterile syringe and small gauge needle. The most effective hemostasis results occur when the THROMBIN-JMI® mixes freely with the blood as soon as it reaches the surface.
3. Sponging of the treated surfaces should be avoided to assure that the clot remains securely in place.

THROMBIN-JMI® may be used in conjunction with Absorbable Gelatin Sponge, USP as follows:
1. Prepare THROMBIN-JMI® solution to desired strength.
2. Immerse sponge strips of the desired size in THROMBIN-JMI® solution. Knead the sponge strips vigorously with moistened, gloved fingers to remove trapped air, thereby facilitating saturation of the sponge.
3. Apply saturated sponge to bleeding area. Hold in place with a pledget of cotton or a small gauze sponge until hemostasis occurs.

HOW SUPPLIED

THROMBIN-JMI® is supplied in the following packages:
NDC 052604-7102-1...5,000 International Unit vial with 5 mL diluent.
NDC 052604-7105-320,000 International Unit vial with 20 mL diluent.
THROMBIN-JMI® Spray Kit is supplied in the following packages:
NDC 052604-7105-220,000 International Unit vial with 20 mL diluent, spray pump and actuator.
THROMBIN-JMI® Syringe Spray Kit is supplied in the following packages:
NDC 052604-7355-220,000 International Unit vial with 20 mL diluent, spray tip and syringe.

STORAGE

Store THROMBIN-JMI® at 2°-25°C (36°-77°F).
Prescribing Information as of May 2005.
Distributed By:
Jones Pharma Incorporated
Bristol, VA 24201
Manufactured by:
GenTrac, Incorporated
Middleton, Wisconsin 53562
U.S. License No. 977
Shown in Product Identification Guide, page 319

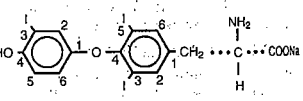
TRIOSTAT®

[trī-ō-stăt]
brand of
liothyronine sodium
injection (T_3)

DESCRIPTION

Thyroid hormone drugs are natural or synthetic preparations containing tetraiodothyronine (T_4, levothyroxine) sodium or triiodothyronine (T_3, liothyronine) sodium or both. T_4 and T_3 are produced in the human thyroid gland by the iodination and coupling of the amino acid tyrosine. T_4 contains four iodine atoms and is formed by the coupling of two molecules of diiodotyrosine (DIT). T_3 contains three atoms of iodine and is formed by the coupling of one molecule of DIT with one molecule of monoiodotyrosine (MIT). Both hormones are stored in the thyroid colloid as thyroglobulin and released into the circulation. The major source of T_3 has been shown to be peripheral deiodination of T_4. T_3 is bound less firmly than T_4 in the serum, enters peripheral tissues more readily, and binds to specific nuclear receptor(s) to initiate hormonal, metabolic effects. T_4 is the prohormone which is deiodinated to T_3 for hormone activity.
Thyroid hormone preparations belong to two categories: (1) natural hormonal preparations derived from animal thyroid, and (2) synthetic preparations. Natural preparations include desiccated thyroid and thyroglobulin. Desiccated thyroid is derived from domesticated animals that are used for food by man (either beef or hog thyroid), and thyroglobulin is derived from thyroid glands of the hog.
Triostat (liothyronine sodium injection) (T_3) contains liothyronine (L-triiodothyronine or L-T_3), a synthetic form of natural thyroid hormone, as the sodium salt.
The structural and empirical formulas and molecular weight of liothyronine sodium are given below.

Liothyronine Sodium



$C_{15}H_{11}I_3NNaO_4$ M.W. 672.96

L-Tyrosine, *O*-(4-hydroxy-3-iodophenyl)-3,5-diiodo-, monosodium salt

In euthyroid patients, 25 mcg of liothyronine is equivalent to approximately 1 grain of desiccated thyroid or thyroglobulin and 0.1 mg of L-thyroxine.
Each mL of *Triostat* in amber-glass vials contains, in sterile non-pyrogenic aqueous solution, liothyronine sodium equivalent to 10 mcg of liothyronine; alcohol, 6.8% by volume; anhydrous citric acid, 0.175 mg; ammonia, 2.19 mg, as ammonium hydroxide.

HOW SUPPLIED

In packages of six 1 mL vials at a concentration of 10 mcg/mL.
NDC 52604-5210-6
Store between 2° and 8°C (35° and 46°F).
Prescribing Information as of July 2004.
Manufactured for:
Jones Pharma Incorporated
(A wholly owned subsidiary of King Pharmaceuticals, Inc)
St. Louis, MO 63146
Manufactured by:
Parkedale Pharmaceuticals, Inc.
Rochester, MI 48307
5210G030
Shown in Product Identification Guide, page 319

Kos Pharmaℓ Pharmaceuticals, Inc.

1 CEDAR BROOK DRIVE
CRANBURY, NJ 08512

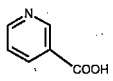
For medical information contact:
Drug Information Services
1-888-454-7437

ADVICOR®

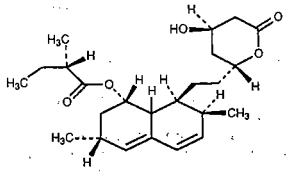
[ad' vĭ kor"]
(niacin extended-release/lovastatin tablets)
℞ Only

DESCRIPTION

ADVICOR contains niacin extended-release and lovastatin in combination. Niacin, a B-complex vitamin, and lovastatin, an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, are both lipid-altering agents.
Niacin is nicotinic acid, or 3-pyridinecarboxylic acid. Niacin is a white, nonhygroscopic crystalline powder that is very soluble in water, boiling ethanol and propylene glycol. It is insoluble in ethyl ether. The empirical formula of niacin is $C_6H_5NO_2$ and its molecular weight is 123.11. Niacin has the following structural formula:



Lovastatin is [1S -[1(alpha)(R *), 3(alpha), 7(beta), 8(beta)(2S *, 4S *), 8a(beta)]]-1,2,3, 7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl 2-methylbutanoate. Lovastatin is a white, nonhygroscopic crystalline powder that is insoluble in water and sparingly soluble in ethanol, methanol, and acetonitrile. The empirical formula of lovastatin is $C_{24}H_{36}O_5$ and its molecular weight is 404.55. Lovastatin has the following structural formula:



ADVICOR tablets contain the labeled amount of niacin and lovastatin and have the following inactive ingredients: hypromellose, povidone, stearic
tanium dioxide, polysorbate
strengths (expressed in terms
contain the following coloring a
ADVICOR 500 mg/20 mg - sy
oxides.
ADVICOR 1000 mg/20 mg -
black iron oxides.

CLINICAL PHARMACOLOG

A variety of clinical studies h
vated levels of total cholesterol
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not been determined.

Effects on Lipids

ADVICOR

ADVICOR reduces LDL-C,
HDL-C due to the indivi
lovastatin. The magnitude o
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underlying lipid abnormality

Niacin

Niacin functions in the bod
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Lovastatin

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Mechanism of Action

Niacin

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Lovastatin

Lovastatin is a specific
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that catalyzes the conver
The conversion of HMG-C
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Pharmacokinetics

Absorption and Bioavail

ADVICOR

In single-dose studies
niacin and lovastatin ab
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release tablets) and Me
tively. After admin
1000 mg/20 mg tablets,
aged about 18 mcg/mL a
ing; about 72% of the nia

hypromellose, povidone, stearic acid, polyethylene glycol, titanium dioxide, polysorbate 80. The individual tablet strengths (expressed in terms of mg niacin/mg lovastatin) contain the following coloring agents:

ADVICOR 500 mg/20 mg - synthetic red and yellow iron oxides.

ADVICOR 1000 mg/20 mg - synthetic red, yellow, and black iron oxides.

CLINICAL PHARMACOLOGY

A variety of clinical studies have demonstrated that elevated levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and apolipoprotein B-100 (Apo B) promote human atherosclerosis. Similarly, decreased levels of high-density lipoprotein cholesterol (HDL-C) are associated with the development of atherosclerosis. Epidemiological investigations have established that cardiovascular morbidity and mortality vary directly with the level of TC and LDL-C, and inversely with the level of HDL-C.

Cholesterol-enriched triglyceride-rich lipoproteins, including very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and their remnants, can also promote atherosclerosis. Elevated plasma triglycerides (TG) are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease (CHD). As such, total plasma TG have not consistently been shown to be an independent risk factor for CHD.

As an adjunct to diet, the efficacy of niacin and lovastatin in improving lipid profiles (either individually, or in combination with each other, or niacin in combination with other statins) for the treatment of dyslipidemia has been well documented. The effect of combined therapy with niacin and lovastatin on cardiovascular morbidity and mortality has not been determined.

Effects on Lipids

ADVICOR

ADVICOR reduces LDL-C, TC, and TG, and increases HDL-C due to the individual actions of niacin and lovastatin. The magnitude of individual lipid and lipoprotein responses may be influenced by the severity and type of underlying lipid abnormality.

Niacin

Niacin functions in the body after conversion to nicotinamide adenine dinucleotide (NAD) in the NAD coenzyme system. Niacin (but not nicotinamide) in gram doses reduces LDL-C, Apo B, Lp(a), TG, and TC, and increases HDL-C. The increase in HDL-C is associated with an increase in apolipoprotein A-I (Apo A-I) and a shift in the distribution of HDL subfractions. These shifts include an increase in the HDL_2:HDL_3 ratio, and an elevation in lipoprotein A-I ($Lp\ A\text{-}I$, an HDL-C particle containing only Apo A-I). In addition, preliminary reports suggest that niacin causes favorable LDL particle size transformations, although the clinical relevance of this effect is not yet clear.

Lovastatin

Lovastatin has been shown to reduce both normal and elevated LDL-C concentrations. Apo B also falls substantially during treatment with lovastatin. Since each LDL-C particle contains one molecule of Apo B, and since little Apo B is found in other lipoproteins, this strongly suggests that lovastatin does not merely cause cholesterol to be lost from LDL-C, but also reduces the concentration of circulating LDL particles. In addition, lovastatin can produce increases of variable magnitude in HDL-C, and modestly reduces VLDL-C and plasma TG. The effects of lovastatin on Lp(a), fibrinogen, and certain other independent biochemical risk markers for coronary heart disease are not well characterized.

Mechanism of Action

Niacin

The mechanism by which niacin alters lipid profiles is not completely understood and may involve several actions, including partial inhibition of release of free fatty acids from adipose tissue, and increased lipoprotein lipase activity (which may increase the rate of chylomicron triglyceride removal from plasma). Niacin decreases the rate of hepatic synthesis of VLDL-C and LDL-C, and does not appear to affect fecal excretion of fats, sterols, or bile acids.

Lovastatin

Lovastatin is a specific inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate. The conversion of HMG-CoA to mevalonate is an early step in the biosynthetic pathway for cholesterol. Lovastatin is a prodrug and has little, if any, activity until hydrolyzed to its active beta-hydroxyacid form, lovastatin acid. The mechanism of the LDL-lowering effect of lovastatin may involve both reduction of VLDL-C concentration and induction of the LDL receptor, leading to reduced production and/or increased catabolism of LDL-C.

Pharmacokinetics

Absorption and Bioavailability

ADVICOR

In single-dose studies of ADVICOR, rate and extent of niacin and lovastatin absorption were bioequivalent under fed conditions to that from NIASPAN® (niacin extended-release tablets) and Mevacor® (lovastatin) tablets, respectively. After administration of two ADVICOR 1000 mg/20 mg tablets, peak niacin concentrations averaged about 18 mcg/mL and occurred about 5 hours after dosing, about 72% of the niacin dose was absorbed according to the urinary excretion data. Peak lovastatin concentrations averaged about 11 ng/mL and occurred about 2 hours after dosing.

The extent of niacin absorption from ADVICOR was increased by administration with food. The administration of two ADVICOR 1000 mg/20 mg tablets under low-fat or high-fat conditions resulted in a 22 to 30% increase in niacin bioavailability relative to dosing under fasting conditions. Lovastatin bioavailability is affected by food. Lovastatin Cmax was increased 48% and 21% after a high- and a low-fat meal, respectively, but the lovastatin AUC was decreased 26% and 24% after a high- and a low-fat meal, respectively, compared to those under fasting conditions.

Niacin

Due to extensive and saturable first-pass metabolism, niacin concentrations in the general circulation are dose dependent and highly variable. Peak steady-state niacin concentrations were 0.6, 4.9, and 15.5 mcg/mL after doses of 1000, 1500, and 2000 mg NIASPAN once daily (given as two 500 mg, two 750 mg, and two 1000 mg tablets, respectively).

Lovastatin

Lovastatin appears to be incompletely absorbed after oral administration. Because of extensive hepatic extraction, the amount of lovastatin reaching the systemic circulation as active inhibitors after oral administration is low (<5%) and shows considerable inter-individual variation. Peak concentrations of active and total inhibitors occur within 2 to 4 hours after Mevacor® administration.

Lovastatin absorption appears to be increased by at least 30% by grapefruit juice; however, the effect is dependent on the amount of grapefruit juice consumed and the interval between grapefruit juice and lovastatin ingestion.

With a once-a-day dosing regimen, plasma concentrations of total inhibitors over a dosing interval achieved a steady-state between the second and third days of therapy and were about 1.5 times those following a single dose of Mevacor®.

Distribution

Niacin

Niacin is less than 20% bound to human serum proteins and distributes into milk. Studies using radiolabeled niacin in mice show that niacin and its metabolites concentrate in the liver, kidney, and adipose tissue.

Lovastatin

Both lovastatin and its beta-hydroxyacid metabolite are highly bound (>95%) to human plasma proteins. Distribution of lovastatin or its metabolites into human milk is unknown; however, lovastatin distributes into milk in rats. In animal studies, lovastatin concentrated in the liver, and crossed the blood-brain and placental barriers.

Metabolism

Niacin

Niacin undergoes rapid and extensive first-pass metabolism that is dose-rate specific and, at the doses used to treat dyslipidemia, saturable. In humans, one pathway is through a simple conjugation step with glycine to form nicotinuric acid (NUA). NUA is then excreted, although there may be a small amount of reversible metabolism back to niacin. The other pathway results in the formation of NAD. It is unclear whether nicotinamide is formed as a precursor to, or following the synthesis of, NAD. Nicotinamide is further metabolized to at least N-methylnicotinamide (MNA) and nicotinamide-N-oxide (NNO). MNA is further metabolized to two other compounds, N-methyl-2-pyridone-5-carboxamide (2PY) and N-methyl-4-pyridone-5-carboxamide (4PY). The formation of 2PY appears to predominate over 4PY in humans.

Lovastatin

Lovastatin undergoes extensive first-pass extraction and metabolism by cytochrome P450 3A4 in the liver, its primary site of action. The major active metabolites present in human plasma are the beta-hydroxyacid of lovastatin (lovastatin acid), its 6'-hydroxy derivative, and two additional metabolites.

Elimination

ADVICOR

Niacin is primarily excreted in urine mainly as metabolites. After a single dose of ADVICOR, at least 60% of the niacin dose was recovered in urine as unchanged niacin and its metabolites. The plasma half-life for lovastatin was about 4.5 hours in single-dose studies.

Niacin

The plasma half-life for niacin is about 20 to 48 minutes after oral administration and dependent on dose administered. Following multiple oral doses of NIASPAN, up to 12% of the dose was recovered in urine as unchanged niacin depending on dose administered. The ratio of metabolites recovered in the urine was also dependent on the dose administered.

Lovastatin

Lovastatin is excreted in urine and bile, based on studies of Mevacor®. Following an oral dose of radiolabeled lovastatin in man, 10% of the dose was excreted in urine and 83% in feces. The latter represents absorbed drug equivalents excreted in bile, as well as any unabsorbed drug.

Special Populations

Hepatic

No pharmacokinetic studies have been conducted in patients with hepatic insufficiency for either niacin or lovastatin (see **WARNINGS, Liver Dysfunction**).

Renal

No information is available on the pharmacokinetics of niacin in patients with renal insufficiency.

In a study of patients with severe renal insufficiency (creatinine clearance 10 to 30 mL/min), the plasma concentrations of total inhibitors after a single dose of lovastatin were approximately two-fold higher than those in healthy volunteers.

ADVICOR should be used with caution in patients with renal disease.

Gender

Plasma concentrations of niacin and metabolites after single- or multiple-dose administration of niacin are generally higher in women than in men, with the magnitude of the difference varying with dose and metabolite. Recovery of niacin and metabolites in urine, however, is generally similar for men and women, indicating similar absorption for both genders. The gender differences observed in plasma niacin and metabolite levels may be due to gender-specific differences in metabolic rate or volume of distribution. Data from clinical trials suggest that women have a greater hypolipidemic response than men at equivalent doses of NIASPAN and ADVICOR.

In a multiple-dose study, plasma concentrations of active and total HMG-CoA reductase inhibitors were 20 to 50% higher in women than in men. In two single-dose studies with ADVICOR, lovastatin concentrations were about 30% higher in women than men, and total HMG-CoA reductase inhibitor concentrations were about 20 to 25% greater in women.

In a multi-center, randomized, double-blind, active-comparator study in patients with Type IIa and IIb hyperlipidemia, ADVICOR was compared to single-agent treatment (NIASPAN and lovastatin). The treatment effects of ADVICOR compared to lovastatin and NIASPAN differed for males and females with a significantly larger treatment effect seen for females. The mean percent change from baseline at endpoint for LDL-C, TG, and HDL-C by gender are as follows (Table 1):

Table 1. Mean percent change from baseline at endpoint for LDL-C, HDL-C and TG by gender

	ADVICOR 2000 mg/40 mg		NIASPAN 2000 mg		Lovastatin 40 mg	
	Women (n=22)	Men (n=30)	Women (n=28)	Men (n=28)	Women (n=21)	Men (n=38)
LDL-C	-47%	-34%	-12%	-9%	-31%	-31%
HDL-C	+33%	+24%	+22%	+15%	+3%	+7%
TG	-48%	-35%	-25%	-15%	-15%	-23%

Clinical Studies

In a multi-center, randomized, double-blind, parallel, 28-week, active-comparator study in patients with Type IIa and IIb hyperlipidemia, ADVICOR was compared to each of its components (NIASPAN and lovastatin). Using a forced dose-escalation study design, patients received each dose for at least 4 weeks. Patients randomized to treatment with ADVICOR initially received 500 mg/20 mg. The dose was increased at 4-week intervals to a maximum of 1000 mg/20 mg in one-half of the patients and 2000 mg/40 mg in the other half. The NIASPAN monotherapy group underwent a similar titration from 500 mg to 2000 mg. The patients randomized to lovastatin monotherapy received 20 mg for 12 weeks titrated to 40 mg for up to 16 weeks. Up to a third of the patients randomized to ADVICOR or NIASPAN discontinued prior to Week 28. In this study, ADVICOR decreased LDL-C, TG and Lp(a), and increased HDL-C in a dose-dependent fashion (Tables 2, 3, 4 and 5 below). Results from this study for LDL-C mean percent change from baseline (the primary efficacy variable) showed that:

1) LDL-lowering with ADVICOR was significantly greater than that achieved with lovastatin 40 mg only after 28 weeks of titration to a dose of 2000 mg/40 mg ($p<.0001$)
2) ADVICOR at doses of 1000 mg/20 mg or higher achieved greater LDL-lowering than NIASPAN ($p<.0001$)

The LDL-C results are summarized in Table 2.

[See table 2 at top of next page]

ADVICOR achieved significantly greater HDL-raising compared to lovastatin and NIASPAN monotherapy at all doses (Table 3).

[See table 3 at top of next page]

In addition, ADVICOR achieved significantly greater TG-lowering at doses of 1000 mg/20 mg or greater compared to lovastatin and NIASPAN monotherapy (Table 4).

[See table 4 at top of next page]

The Lp(a) lowering effects of ADVICOR and NIASPAN were similar, and both were superior to lovastatin (Table 5). The independent effect of lowering Lp(a) with NIASPAN or ADVICOR on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

[See table 5 on next page]

ADVICOR Long-Term Study

A total of 814 patients were enrolled in a long-term (52-week), open-label, single-arm study of ADVICOR. Patients were force dose-titrated to 2000 mg/40 mg over 16 weeks. After titration, patients were maintained on the maximum tolerated dose of ADVICOR for a total of 52 weeks. Five hundred-fifty (550) patients (68%) completed the study, and fifty-six percent (56%) of all patients were able to maintain a dose of 2000 mg/40 mg for the 52 weeks

Continued on next page

Advicor—Cont.

of treatment. The lipid-altering effects of ADVICOR peaked after 4 weeks on the maximum tolerated dose, and were maintained for the duration of treatment. These effects were comparable to what was observed in the double-blind study of ADVICOR (Tables 2-4).

INDICATIONS AND USAGE

ADVICOR is a fixed-dose combination product and is not indicated for initial therapy (see **DOSAGE AND ADMINISTRATION**). Therapy with lipid-altering agents should be only one component of multiple risk-factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Initial medical therapy is indicated with a single agent as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate (see also Table 7 and the NCEP treatment guidelines[1]).

ADVICOR is indicated for the treatment of primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Frederickson Types IIa and IIb; Table 6) in:

- Patients treated with lovastatin who require further TG-lowering or HDL-raising who may benefit from having niacin added to their regimen
- Patients treated with niacin who require further LDL-lowering who may benefit from having lovastatin added to their regimen

Table 6. Classification of Hyperlipoproteinemias

Type	Lipoproteins Elevated	Lipid Elevations	
		Major	Minor
I (rare)	Chylomicrons	TG	↑→TC
IIa	LDL	TC	-
IIb	LDL, VLDL	TC	TG
III (rare)	IDL	TC/TG	-
IV	VLDL	TG	↑→TC
V (rare)	Chylomicrons, VLDL	TG	↑→TC

TC = total cholesterol; TG = triglycerides; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein; IDL = intermediate-density lipoprotein
↑→ = increased or no change

General Recommendations

Prior to initiating therapy with a lipid-lowering agent, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile performed to measure TC, HDL-C, and TG. For patients with TG < 400 mg/dL, LDL-C can be estimated using the following equation:

$$LDL\text{-}C = TC - [(0.20 \times TG) + HDL\text{-}C]$$

For TG levels > 400 mg/dL, this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. Lipid determinations should be performed at intervals of no less than 4 weeks and dosage adjusted according to the patient's response to therapy. The NCEP Treatment Guidelines are summarized in Table 7.

[See table 7 at right]

After the LDL-C goal has been achieved, if the TG is still ≥ 200 mg/dL, non-HDL-C (TC minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

CONTRAINDICATIONS

ADVICOR is contraindicated in patients with a known hypersensitivity to niacin, lovastatin or any component of this medication, active liver disease or unexplained persistent elevations in serum transaminases (see **WARNINGS**), active peptic ulcer disease, or arterial bleeding.

Pregnancy and lactation—Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase, such as lovastatin, to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, ADVICOR is contraindicated in women who are pregnant and in lactating mothers. ADVICOR may cause fetal harm when administered to pregnant women. **ADVICOR should be administered to women of childbearing age only when such patients are highly unlikely to conceive.** If the patient becomes pregnant while taking this drug, ADVICOR should be discontinued immediately and the patient should be apprised of the potential hazard to the fetus (see **PRECAUTIONS, Pregnancy**).

WARNINGS

ADVICOR should not be substituted for equivalent doses of immediate-release (crystalline) niacin. For patients switching from immediate-release niacin to NIASPAN, therapy with NIASPAN should be initiated with low doses (i.e., 500 mg once daily at bedtime) and the NIASPAN dose should then be titrated to the desired therapeutic response (see DOSAGE AND ADMINISTRATION).

Table 2. LDL-C mean percent change from baseline

Week	ADVICOR			NIASPAN			Lovastatin		
	n*	Dose (mg/mg)	LDL	n*	Dose (mg)	LDL	n*	Dose (mg)	LDL
Baseline	57	-	190.9 mg/dL	61	-	189.7 mg/dL	61	-	185.6 mg/dL
12	47	1000/20	-30%	46	1000	-3%	56	20	-29%
16	45	1000/40	-36%	44	1000	-6%	56	40	-31%
20	42	1500/40	-37%	43	1500	-12%	54	40	-34%
28	42	2000/40	-42%	41	2000	-14%	53	40	-32%

*n = number of patients remaining in the trial at each timepoint

Table 3. HDL-C mean percent change from baseline

Week	ADVICOR			NIASPAN			Lovastatin		
	n*	Dose (mg/mg)	HDL	n*	Dose (mg)	HDL	n*	Dose (mg)	HDL
Baseline	57	-	45 mg/dL	61	-	47 mg/dL	61	-	43 mg/dL
12	47	1000/20	+20%	46	1000	+14%	56	20	+3%
16	45	1000/40	+20%	44	1000	+15%	56	40	+5%
20	42	1500/40	+27%	43	1500	+22%	54	40	+6%
28	42	2000/40	+30%	41	2000	+24%	53	40	+6%

*n = number of patients remaining in the trial at each timepoint

Table 4. TG median percent change from baseline

Week	ADVICOR			NIASPAN			Lovastatin		
	n*	Dose (mg/mg)	TG	n*	Dose (mg)	TG	n*	Dose (mg)	TG
Baseline	57	-	174 mg/dL	61	-	186 mg/dL	61	-	171 mg/dL
12	47	1000/20	-32%	46	1000	-22%	56	20	-20%
16	45	1000/40	-39%	44	1000	-23%	56	40	-17%
20	42	1500/40	-44%	43	1500	-31%	54	40	-21%
28	42	2000/40	-44%	41	2000	-31%	53	40	-20%

*n = number of patients remaining in the trial at each timepoint

Table 5. Lp(a) median percent change from baseline

Week	ADVICOR			NIASPAN			Lovastatin		
	n*	Dose (mg/mg)	Lp(a)	n*	Dose (mg)	Lp(a)	n*	Dose (mg)	Lp(a)
Baseline	57	-	34 mg/dL	61	-	41 mg/dL	60	-	42 mg/dL
12	47	1000/20	-9%	46	1000	-8%	55	20	+8%
16	45	1000/40	-9%	44	1000	-12%	55	40	+8%
20	42	1500/40	-17%	43	1500	-22%	53	40	+6%
28	42	2000/40	-22%	41	2000	-32%	52	40	0%

*n = number of patients remaining in the trial at each timepoint

Table 7. NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD† or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional)††
2+ Risk factors (10-year risk ≤20%)	<130	≥130	10-year risk 10%-20%:≥130 10-year risk <10%:≥160
0-1 Risk factor†††	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

†CHD, coronary heart disease
††Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, i.e., nicotinic acid or fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.
†††Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

Liver Dysfunction

Cases of severe hepatic toxicity, including fulminant hepatic necrosis, have occurred in patients who have substituted sustained-release (modified-release, timed-release) niacin products for immediate-release (crystalline) niacin at equivalent doses.

ADVICOR should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of ADVICOR.

Niacin preparations and lovastatin preparations have been associated with abnormal liver tests. In studies using NIASPAN alone, 0.8% of patients were discontinued for transaminase elevations. In studies using lovastatin alone, 0.2% of patients were discontinued for transaminase elevations.[2] In three safety and efficacy studies involving titration to final daily ADVICOR doses ranging from 500 mg/10 mg to 2500 mg/40 mg, ten of 1028 patients (1.0%) experienced reversible elevations in AST/ALT to more than 3 times the upper limit of normal (ULN). Three of ten elevations occurred at doses outside the recommended dosing limit of 2000 mg/40 mg; no patient receiving 1000 mg/20 mg had 3-fold elevations in AST/ALT.

In clinical studies with ADVICOR, elevations in transaminases did not appear to be related to treatment duration; elevations in AST and ALT levels did appear to be dose related. Transaminase elevations were reversible upon discontinuation of ADVICOR.

Liver function tests should be performed on all patients during therapy with ADVICOR. Serum transaminase levels, including AST and ALT (SGOT and SGPT), should be moni-

tured before treatment begins, eve
first 6 months, and periodically th
mately 6-month intervals). Special
to patients who develop elevate
levels, and in these patients, mea
peated promptly and, if confirme
frequently. If the transaminase
progression, particularly if they ris
persistent, or if they are associate
hea, fever, and/or malaise, the dru

Skeletal Muscle

Lovastatin

Lovastatin and other inhibitors o
casionally cause myopathy, which
pain or weakness associated with
ase (> 10 times ULN).

Rhabdomyolysis, with or with
secondary to myoglobinuria, has
can occur at any time. In a large
and efficacy study (the EXCEL
myopathy occurred in up to 0.29
lovastatin 20 to 80 mg for up to
ment was interrupted or discon
muscle symptoms and creatin
promptly resolved. The risk of
concomitant therapy with certain
excluded by the EXCEL study de
The risk of myopathy appears to
of HMG-CoA reductase inhibi
Lovastatin is metabolized by the
3A4. Certain drugs which share
raise the plasma levels of lovast
risk of myopathy. These include
bioconazole and other antifung
tibiotics erythromycin and clarit
hibitors, the antidepressant nefa
of grapefruit juice (>1 quart dai

ADVICOR

Myopathy and/or rhabdomyo
when lovastatin is used in com
doses (≥1g/day) of niacin. Ph
use of ADVICOR, a combinatio
should weigh the potential ben
carefully monitor patients for
muscle pain, tenderness, or w
the initial month of treatment
ward dosage titration of either
nations may be considered in
no assurance that such monito
In clinical studies, no cases of
pected case of myopathy have
tients who were treated with
2000 mg/40 mg for periods up
Patients starting therapy with
of the risk of myopathy, and t
plained muscle pain, tenderne
above 10 times ULN in a pati
symptoms indicates myopath
be discontinued if myopathy
In patients with complicated r
to rhabdomyolysis, such as p
dose escalation requires ca
known adverse consequences
apy, treatment with ADVICO
days before elective major s
acute medical or surgical con

Use of ADVICOR with other

The incidence and severity o
by concomitant administra
that can cause myopathy wh
fibrozil and other fibrates.
The use of ADVICOR in com
be avoided unless the benef
levels is likely to outweigh
combination. In patients tak
or fibrates, the dose of ADV
ceed 1000 mg/20 mg (see D
TION), **as the risk of myo**
doses. Interruption of ADVI
treatment with a systemic
antibiotic should be conside

PRECAUTIONS

General

Before instituting therapy
an attempt should be made
propriate diet, exercise, an
tients, and to treat other u

INDICATIONS AND USA

Patients with a past histor
ease, or peptic ulcer sho
ADVICOR therapy. Frequ
tests and blood glucose sh
that the drug is producing
systems.

Diabetic patients may expe
ing blood sugar (FBS). In
cluded 1028 patients exp
whom had diabetes type
above normal occurred in
during study treatment w
(1.4%) were discontinued
for worsening diabetes, 10
patient for a new diagnos

tovastatin

ose LDL
ng)

- 185.6 mg/dL
20 -29%
40 -31%
40 -34%
40 -32%

Lovastatin

Dose HDL
mg)

- 43 mg/dL
20 +3%
40 +5%
40 +6%
40 +6%

Lovastatin

Dose TG
(mg)

- 171 mg/dL
20 -20%
40 -17%
40 -21%
40 -20%

Lovastatin

Dose Lp(a)
(mg)

- 42 mg/dL
20 +8%
40 +8%
40 +6%
40 0%

style Changes and

L Level at Which to Consider Drug Therapy (mg/dL)

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)-129: drug optional)††

ar risk 10%-20%:≥130

year risk <10%:≥160

≥190
30-189: LDL-lowering drug optional)

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tored before treatment begins, every 6 to 12 weeks for the first 6 months, and periodically thereafter (e.g., at approximately 6-month intervals). Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and, if confirmed, then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times ULN and are persistent, or if they are associated with symptoms of nausea, fever, and/or malaise, the drug should be discontinued.

Skeletal Muscle

Lovastatin

Lovastatin and other inhibitors of HMG-CoA reductase occasionally cause myopathy, which is manifested as muscle pain or weakness associated with grossly elevated creatine kinase (> 10 times ULN).

Rhabdomyolysis, with or without acute renal failure secondary to myoglobinuria, has been reported rarely and can occur at any time. In a large, long-term, clinical safety and efficacy study (the EXCEL study)[3,4] with lovastatin, myopathy occurred in up to 0.2% of patients treated with lovastatin 20 to 80 mg for up to 2 years. When drug treatment was interrupted or discontinued in these patients, muscle symptoms and creatine kinase (CK) increases promptly resolved. The risk of myopathy is increased by concomitant therapy with certain drugs, some of which were excluded by the EXCEL study design.

The risk of myopathy appears to be increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Lovastatin is metabolized by the cytochrome P450 isoform 3A4. Certain drugs which share this metabolic pathway can raise the plasma levels of lovastatin and may increase the risk of myopathy. These include cyclosporine, itraconazole, ketoconazole and other antifungal azoles, the macrolide antibiotics erythromycin and clarithromycin, HIV protease inhibitors, the antidepressant nefazodone, or large quantities of grapefruit juice (>1 quart daily).

ADVICOR

Myopathy and/or rhabdomyolysis have been reported when lovastatin is used in combination with lipid-altering doses (≥1g/day) of niacin. Physicians contemplating the use of ADVICOR, a combination of lovastatin and niacin, should weigh the potential benefits and risks, and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial month of treatment or during any period of upward dosage titration of either drug. Periodic CK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent myopathy. In clinical studies, no cases of rhabdomyolysis and one suspected case of myopathy have been reported in 1079 patients who were treated with ADVICOR at doses up to 1000 mg/40 mg for periods up to 2 years.

Patients starting therapy with ADVICOR should be advised of the risk of myopathy, and told to report promptly unexplained muscle pain, tenderness, or weakness. A CK level above 10 times ULN in a patient with unexplained muscle symptoms indicates myopathy. ADVICOR therapy should be discontinued if myopathy is diagnosed or suspected.

In patients with complicated medical histories predisposing to rhabdomyolysis, such as preexisting renal insufficiency, dose escalation requires caution. Also, as there are no known adverse consequences of brief interruption of therapy, treatment with ADVICOR should be stopped for a few days before elective major surgery and when any major acute medical or surgical condition supervenes.

Use of ADVICOR with other Drugs

The incidence and severity of myopathy may be increased by concomitant administration of ADVICOR with drugs that can cause myopathy when given alone, such as gemfibrozil and other fibrates.

The use of ADVICOR in combination with fibrates should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination. In patients taking concomitant cyclosporine or fibrates, the dose of ADVICOR should generally not exceed 1000 mg/20 mg (see DOSAGE AND ADMINISTRATION), as the risk of myopathy may increase at higher doses. Interruption of ADVICOR therapy during a course of treatment with a systemic antifungal azole or a macrolide antibiotic should be considered.

PRECAUTIONS

General

Before instituting therapy with a lipid-altering medication, an attempt should be made to control dyslipidemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE).

Patients with a past history of jaundice, hepatobiliary disease, or peptic ulcer should be observed closely during ADVICOR therapy. Frequent monitoring of liver function tests and blood glucose should be performed to ascertain that the drug is producing no adverse effects on these organ systems.

Diabetic patients may experience a dose-related rise in fasting blood sugar (FBS). In three clinical studies, which included 1028 patients exposed to ADVICOR (6 to 22% of whom had diabetes type II at baseline), increases in FBS above normal occurred in 46 to 65% of patients at any time during study treatment with ADVICOR. Fourteen patients (1.4%) were discontinued from study treatment: 3 patients for worsening diabetes, 10 patients for hyperglycemia and 1 patient for a new diagnosis of diabetes. In the studies in which lovastatin and NIASPAN were used as active controls, 24 to 41% of patients receiving lovastatin and 43 to 58% of patients receiving NIASPAN also had increases in FBS above normal. One patient (1.1%) receiving lovastatin was discontinued for hyperglycemia. Diabetic or potentially diabetic patients should be observed closely during treatment with ADVICOR, and adjustment of diet and/or hypoglycemic therapy may be necessary.

In one long-term study of 106 patients treated with ADVICOR, elevations in prothrombin time (PT) >3 times ULN occurred in 2 patients (2%) during study drug treatment. In a long-term study of 814 patients treated with ADVICOR, 7 patients were noted to have platelet counts <100,000 during study drug treatment. Four of these patients were discontinued, and one patient with a platelet count <100,000 had prolonged bleeding after a tooth extraction. Prior studies have shown that NIASPAN can be associated with dose-related reductions in platelet count (mean of -11% with 2000 mg) and increases of PT (mean of approximately +4%). Accordingly, patients undergoing surgery should be carefully evaluated. In controlled studies, ADVICOR has been associated with small but statistically significant dose-related reductions in phosphorus levels (mean of -10% with 2000 mg/40 mg). Phosphorus levels should be monitored periodically in patients at risk for hypophosphatemia. In clinical studies with ADVICOR, hypophosphatemia was more common in males than in females. The clinical relevance of hypophosphatemia in this population is not known.

Niacin

Caution should also be used when ADVICOR is used in patients with unstable angina or in the acute phase of MI, particularly when such patients are also receiving vasoactive drugs such as nitrates, calcium channel blockers, or adrenergic blocking agents.

Elevated uric acid levels have occurred with niacin therapy; therefore, in patients predisposed to gout, niacin therapy should be used with caution. Niacin is rapidly metabolized by the liver, and excreted through the kidneys. ADVICOR is contraindicated in patients with significant or unexplained hepatic dysfunction (see **CONTRAINDICATIONS** and **WARNINGS**) and should be used with caution in patients with renal dysfunction.

Lovastatin

Lovastatin may elevate creatine phosphokinase and transaminase levels (see **WARNINGS** and **ADVERSE REACTIONS**). This should be considered in the differential diagnosis of chest pain in a patient on therapy with lovastatin.

Endocrine function—HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Results of clinical studies with drugs in this class have been inconsistent with regard to drug effects on basal and reserve steroid levels. However, clinical studies have shown that lovastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve, and does not reduce basal plasma testosterone concentration. Another HMG-CoA reductase inhibitor has been shown to reduce the plasma testosterone response to human chorionic gonadotropin (HCG). In the same study, the mean testosterone response to HCG was slightly but not significantly reduced after treatment with lovastatin 40 mg daily for 16 weeks in 21 men. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of male patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Patients treated with lovastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

CNS toxicity—Lovastatin produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). Vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis were also seen in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level (Cmax) similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits and necrosis of small vessels, were seen in dogs treated with lovastatin at a dose of 180 mg/kg/day, a dose which produced plasma drug levels (Cmax) which were about 30 times higher than the mean values in humans taking 80 mg/day.

Similar optic nerve and CNS vascular lesions have been observed with other drugs of this class.

Cataracts were seen in dogs treated with lovastatin for 11 and 28 weeks at 180 mg/kg/day and 1 year at 60 mg/kg/day.

Information for Patients

Patients should be advised of the following:

— to report promptly unexplained muscle pain, tenderness, or weakness (see **WARNINGS, Skeletal Muscle**);
— to take ADVICOR at bedtime, with a low-fat snack. Administration on an empty stomach is not recommended;
— to carefully follow the prescribed dosing regimen (see **DOSAGE AND ADMINISTRATION**);
— that flushing is a common side effect of niacin therapy that usually subsides after several weeks of consistent niacin use. Flushing may last for several hours after dosing, may vary in severity, and will, by taking ADVICOR at bedtime, most likely occur during sleep. If awakened by flushing, especially if taking antihypertensives, rise slowly to minimize the potential for dizziness and/or syncope;
— that taking aspirin (up to approximately 30 minutes before taking ADVICOR) or another non-steroidal anti-inflammatory drug (e.g., ibuprofen) may minimize flushing;
— to avoid ingestion of alcohol or hot drinks around the time of ADVICOR administration, to minimize flushing;
— should not be administered with grapefruit juice;
— that if ADVICOR therapy is discontinued for an extended length of time, their physician should be contacted prior to re-starting therapy; re-titration is recommended (see **DOSAGE AND ADMINISTRATION**);
— to notify their physician if they are taking vitamins or other nutritional supplements containing niacin or related compounds such as nicotinamide (see **Drug Interactions**);
— to notify their physician if symptoms of dizziness occur;
— if diabetic, to notify their physician of changes in blood glucose;
— that ADVICOR tablets should not be broken, crushed, or chewed, but should be swallowed whole.

Drug Interactions

Niacin

Antihypertensive Therapy—Niacin may potentiate the effects of ganglionic blocking agents and vasoactive drugs resulting in postural hypotension.

Aspirin: Concomitant aspirin may decrease the metabolic clearance of niacin. The clinical relevance of this finding is unclear.

Bile Acid Sequestrants—An *in vitro* study was carried out investigating the niacin-binding capacity of colestipol and cholestyramine. About 98% of available niacin was bound to colestipol, with 10 to 30% binding to cholestyramine. These results suggest that 4 to 6 hours, or as great an interval as possible, should elapse between the ingestion of bile acid-binding resins and the administration of ADVICOR.

Other—Concomitant alcohol or hot drinks may increase the side effects of flushing and pruritus and should be avoided around the time of ADVICOR ingestion. Vitamins or other nutritional supplements containing large doses of niacin or related compounds such as nicotinamide may potentiate the adverse effects of ADVICOR.

Lovastatin

Serious skeletal muscle disorders, e.g., rhabdomyolysis, have been reported during concomitant therapy of lovastatin or other HMG-CoA reductase inhibitors with cyclosporine, itraconazole, ketoconazole, gemfibrozil, niacin, erythromycin, clarithromycin, nefazodone or HIV protease inhibitors. (See **WARNINGS, Skeletal Muscle**).

Coumarin Anticoagulants—In a small clinical study in which lovastatin was administered to warfarin-treated patients, no effect on PT was detected. However, another HMG-CoA reductase inhibitor has been found to produce a less than two seconds increase in PT in healthy volunteers receiving low doses of warfarin. Also, bleeding and/or increased PT have been reported in a few patients taking coumarin anticoagulants concomitantly with lovastatin. It is recommended that in patients taking anticoagulants, PT be determined before starting ADVICOR and frequently enough during early therapy to insure that no significant alteration of PT occurs. Once a stable PT has been documented, PT can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of ADVICOR is changed, the same procedure should be repeated.

Antipyrine—Lovastatin had no effect on the pharmacokinetics of antipyrine or its metabolites. However, since lovastatin is metabolized by the cytochrome P450 isoform 3A4 enzyme system, this does not preclude an interaction with other drugs metabolized by the same isoform.

Propranolol—In normal volunteers, there was no clinically significant pharmacokinetic or pharmacodynamic interaction with concomitant administration of single doses of lovastatin and propranolol.

Digoxin—In patients with hypercholesterolemia, concomitant administration of lovastatin and digoxin resulted in no effect on digoxin plasma concentrations.

Oral Hypoglycemic Agents—In pharmacokinetic studies of lovastatin in hypercholesterolemic, non-insulin dependent diabetic patients, there was no drug interaction with glipizide or with chlorpropamide.

Drug/Laboratory Test Interactions

Niacin may produce false elevations in some fluorometric determinations of plasma or urinary catecholamines. Niacin may also give false-positive reactions with cupric sulfate solution (Benedict's reagent) in urine glucose tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted with ADVICOR regarding carcinogenesis, mutagenesis, or impairment of fertility.

Niacin

Niacin, administered to mice for a lifetime as a 1% solution in drinking water, was not carcinogenic. The mice in this study received approximately 6 to 8 times a human dose of 3000 mg/day as determined on a mg/m^2 basis. Niacin was negative for mutagenicity in the Ames test. No studies on impairment of fertility have been performed.

Continued on next page

Advicor—Cont.

Lovastatin

In a 21-month carcinogenic study in mice, there was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in both males and females at 500 mg/kg/day. This dose produced a total plasma drug exposure 3 to 4 times that of humans given the highest recommended dose of lovastatin (drug exposure was measured as total HMG-CoA reductase inhibitory activity in extracted plasma). Tumor increases were not seen at 20 and 100 mg/kg/day, doses that produced drug exposures of 0.3 to 2 times that of humans at the 80 mg/day dose. A statistically significant increase in pulmonary adenomas was seen in female mice at approximately 4 times the human drug exposure. (Although mice were given 300 times the human dose on a mg/kg body weight basis, plasma levels of total inhibitory activity were only 4 times higher in mice than in humans given 80 mg of lovastatin.)

There was an increase in incidence of papilloma in the nonglandular mucosa of the stomach of mice beginning at exposures of 1 to 2 times that of humans. The glandular mucosa was not affected. The human stomach contains only glandular mucosa.

In a 24-month carcinogenicity study in rats, there was a positive dose-response relationship for hepatocellular carcinogenicity in males at drug exposures between 2 to 7 times that of human exposure at 80 mg/day (doses in rats were 5, 30, and 180 mg/kg/day).

An increased incidence of thyroid neoplasms in rats appears to be a response that has been seen with other HMG-CoA reductase inhibitors.

A drug in this class chemically similar to lovastatin was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat or mouse hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

Drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation were seen in dogs starting at 20 mg/kg/day. Similar findings were seen with another drug in this class. No drug-related effects on fertility were found in studies with lovastatin in rats. However, in studies with a similar drug in this class, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. No microscopic changes were observed in the testes from rats of either study. The clinical significance of these findings is unclear.

Pregnancy

Pregnancy Category X—See **CONTRAINDICATIONS**.

ADVICOR should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazard. Safety in pregnant women has not been established and there is no apparent benefit to therapy with ADVICOR during pregnancy (see **CONTRAINDICATIONS**). Treatment should be immediately discontinued as soon as pregnancy is recognized.

Niacin

Animal reproduction studies have not been conducted with niacin or with ADVICOR. It is also not known whether niacin at doses typically used for lipid disorders can cause fetal harm when administered to pregnant women or whether it can affect reproductive capacity. If a woman receiving niacin or ADVICOR for primary hypercholesterolemia (Types IIa or IIb) becomes pregnant, the drug should be discontinued.

Lovastatin

Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. In a review[5] of approximately 100 prospectively followed pregnancies in women exposed to lovastatin or another structurally related HMG-CoA reductase inhibitor, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a 3- to 4-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. Lovastatin has been shown to produce skeletal malformations at plasma levels 40 times the human exposure (for mouse fetus) and 80 times the human exposure (for rat fetus) based on mg/m^2 surface area (doses were 800 mg/kg/day). No drug-induced changes were seen in either species at multiples of 8 times (rat) or 4 times (mouse) based on surface area. No evidence of malformations was noted in rabbits at exposures up to 3 times the human exposure (dose of 15 mg/kg/day, highest tolerated dose).

Labor and Delivery

No studies have been conducted on the effect of ADVICOR, niacin or lovastatin on the mother or the fetus during labor or delivery, on the duration of labor or delivery, or on the growth, development, and functional maturation of the child.

Nursing Mothers

No studies have been conducted with ADVICOR in nursing mothers.

Because of the potential for serious adverse reactions in nursing infants from lipid-altering doses of niacin and lovastatin (see **CONTRAINDICATIONS**), ADVICOR should not be taken while a woman is breastfeeding.

Niacin has been reported to be excreted in human milk. It is not known whether lovastatin is excreted in human milk. A small amount of another drug in this class is excreted in human breast milk.

Table 8. Treatment-Emergent Adverse Events in ≥ 5% of Patients
(Events Irrespective of Causality; Data from Controlled, Double-Blind Studies)

Adverse Event	ADVICOR	NIASPAN	Lovastatin
Total Number of Patients	214	92	94
Cardiovascular	**163 (76%)**	**66 (72%)**	**24 (26%)**
Flushing	152 (71%)	60 (65%)	17 (18%)
Body as a Whole	**104 (49%)**	**50 (54%)**	**42 (45%)**
Asthenia	10 (5%)	6 (7%)	5 (5%)
Flu Syndrome	12 (6%)	7 (8%)	4 (4%)
Headache	20 (9%)	12 (13%)	5 (5%)
Infection	43 (20%)	14 (15%)	19 (20%)
Pain	18 (8%)	3 (3%)	9 (10%)
Pain, Abdominal	9 (4%)	1 (1%)	6 (6%)
Pain, Back	10 (5%)	5 (5%)	5 (5%)
Digestive System	**51 (24%)**	**26 (28%)**	**16 (17%)**
Diarrhea	13 (6%)	8 (9%)	2 (2%)
Dyspepsia	6 (3%)	5 (5%)	4 (4%)
Nausea	14 (7%)	11 (12%)	2 (2%)
Vomiting	7 (3%)	5 (5%)	0
Metabolic and Nutrit. System	**37 (17%)**	**18 (20%)**	**13 (14%)**
Hyperglycemia	8 (4%)	6 (7%)	6 (6%)
Musculoskeletal System	**19 (9%)**	**9 (10%)**	**17 (18%)**
Myalgia	6 (3%)	5 (5%)	8 (9%)
Skin and Appendages	**3 (2%)**	**19 (21%)**	**11 (12%)**
Pruritus	14 (7%)	7 (8%)	3 (3%)
Rash	11 (5%)	11 (12%)	3 (3%)

Note: Percentages are calculated from the total number of patients in each column.

Pediatric use

No studies in patients under 18 years-of-age have been conducted with ADVICOR. Because pediatric patients are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug or its active ingredients is limited, treatment of pediatric patients with ADVICOR is not recommended at this time.

Geriatric Use

Of the 214 patients who received ADVICOR in double-blind clinical studies, 37.4% were 65 years-of-age and older, and of the 814 patients who received ADVICOR in open-label clinical studies, 36.2% were 65 years-of-age and older. Responses in LDL-C, HDL-C, and TG were similar in geriatric patients. No overall differences in the percentage of patients with adverse events were observed between older and younger patients. No overall differences were observed in selected chemistry values between the two groups except for amylase which was higher in older patients.

ADVERSE REACTIONS

Overview

In controlled clinical studies, 40/214 (19%) of patients randomized to ADVICOR discontinued therapy prior to study completion, 18/214 (8%) of discontinuations being due to flushing. In the same controlled studies, 9/94 (10%) of patients randomized to lovastatin and 19/92 (21%) of patients randomized to NIASPAN also discontinued treatment prior to study completion secondary to adverse events. Flushing episodes (i.e., warmth, redness, itching and/or tingling) were the most common treatment-emergent adverse events and occurred in 53% to 83% of patients treated with ADVICOR. Spontaneous reports with NIASPAN and clinical studies with ADVICOR suggest that flushing may also be accompanied by symptoms of dizziness or syncope, tachycardia, palpitations, shortness of breath, sweating, chills and/or edema.

Adverse Reactions Information

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice. The adverse reaction information from clinical studies does, however provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

The data described in this section reflect the exposure to ADVICOR in two double-blind, controlled clinical studies of 400 patients. The population was 28 to 86 years-of-age, 54% male, 85% Caucasian, 9% Black, and 7% Other, and had mixed dyslipidemia (Frederickson Types IIa and IIb).

In addition to flushing, other adverse events occurring in 5% or greater of patients treated with ADVICOR are shown in Table 8 below.

[See table 8 below]

The following adverse events have also been reported with niacin, lovastatin, and/or other HMG-CoA reductase inhibitors, but not necessarily with ADVICOR, either during clinical studies or in routine patient management.

Body as a Whole:	chest pain; abdominal pain; edema; chills; malaise
Cardiovascular:	atrial fibrillation; tachycardia; palpitations, and other cardiac arrhythmias; orthostasis hypotension; syncope
Eye:	toxic amblyopia; cystoid macular edema; ophthalmoplegia; eye irritation
Gastrointestinal:	activation of peptic ulcers and peptic ulceration; dyspepsia; vomiting; anorexia; constipation; flatulence, pancreatitis; hepatitis; fatty change in liver; jaundice; and rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma
Metabolic:	gout
Musculoskeletal:	muscle cramps; myopathy; rhabdomyolysis; arthralgia
Nervous:	dizziness; insomnia; dry mouth; paresthesia; anxiety; tremor; vertigo; memory loss; peripheral neuropathy; psychic disturbances; dysfunction of certain cranial nerves
Skin:	hyper-pigmentation; acanthosis nigricans; urticaria; alopecia; dry skin; sweating; and a variety of skin changes (e.g., nodules, discoloration, dryness of mucous membranes, changes to hair/nails)
Respiratory:	dyspnea; rhinitis
Urogenital:	gynecomastia; loss of libido; erectile dysfunction
Hypersensitivity reactions:	An apparent hypersensitivity syndrome has been reported rarely, which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia,

Other:

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abdomyolysis; arthralgia
zziness; insomnia; dry
outh; paresthesia; anxiety;
mor; vertigo; memory loss;
ripheral neuropathy; psy-
ic disturbances; dysfunction
certain cranial nerves
per-pigmentation; acantho-
s nigricans; urticaria; alope-
a; dry skin; sweating; and a
riety of skin changes (e.g.,
odules, discoloration, dry-
ess of mucous membranes,
anges to hair/nails)
spnea; rhinitis
necomastia; loss of libido;
ectile dysfunction
n apparent hypersensitivity
ndrome has been reported
rely, which has included one
more of the following fea-
res: anaphylaxis, angio-
lema, lupus erythematosus-
ke syndrome, polymyalgia
heumatica, vasculitis, pur-
ura, thrombocytopenia, leu-
openia, hemolytic anemia,

positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Other: migraine

Clinical Laboratory Abnormalities

Chemistry

Elevations in serum transaminases (see **WARNINGS - Liver Dysfunction**), CPK and fasting glucose, and reductions in phosphorus. Niacin extended-release tablets have been associated with slight elevations in LDH, uric acid, total bilirubin, and amylase. Lovastatin and/or HMG-CoA reductase inhibitors have been associated with elevations in alkaline phosphatase, γ-glutamyl transpeptidase and bilirubin, and thyroid function abnormalities.

Hematology

Niacin extended-release tablets have been associated with slight reductions in platelet counts and prolongation in PT (see **WARNINGS**).

DRUG ABUSE AND DEPENDENCE

Neither niacin nor lovastatin is a narcotic drug. ADVICOR has no known addiction potential in humans.

OVERDOSAGE

Information on acute overdose with ADVICOR in humans is limited. Until further experience is obtained, no specific treatment of overdose with ADVICOR can be recommended. The patient should be carefully observed and given supportive treatment.

Niacin

The s.c. LD50 of niacin is 5 g/kg in rats.

The signs and symptoms of an acute overdose of niacin can be anticipated to be those of excessive pharmacologic effect: severe flushing, nausea/vomiting, diarrhea, dyspepsia, dizziness, syncope, hypotension, possibly cardiac arrhythmias and clinical laboratory abnormalities. Insufficient information is available on the potential for the dialyzability of niacin.

Lovastatin

After oral administration of lovastatin to mice the median lethal dose observed was >15 g/m^2.

Five healthy human volunteers have received up to 200 mg of lovastatin as a single dose without clinically significant adverse experiences. A few cases of accidental overdose have been reported; no patients had any specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 5 to 6 g. The dialyzability of lovastatin and its metabolites in man is not known at present.

DOSAGE AND ADMINISTRATION

The usual recommended starting dose for NIASPAN is 500 mg qhs. NIASPAN must be titrated and the dose should not be increased by more than 500 mg every 4 weeks up to a maximum dose of 2000 mg a day, to reduce the incidence and severity of side effects. Patients already receiving a stable dose of NIASPAN may be switched directly to a niacin-equivalent dose of ADVICOR.

The usual recommended starting dose of lovastatin is 20 mg once a day. Dose adjustments should be made at intervals of 4 weeks or more. Patients already receiving a stable dose of lovastatin may receive concomitant dosage titration with NIASPAN, and switch to ADVICOR once a stable dose of NIASPAN has been reached.

Flushing of the skin (see **ADVERSE REACTIONS**) may be reduced in frequency or severity by pretreatment with aspirin (taken up to approximately 30 minutes prior to ADVICOR dose) or other non-steroidal anti-inflammatory drugs. Flushing, pruritus, and gastrointestinal distress are also greatly reduced by slowly increasing the dose of niacin and avoiding administration on an empty stomach.

Equivalent doses of ADVICOR may be substituted for equivalent doses of NIASPAN but should not be substituted for other modified-release (sustained-release or time-release) niacin preparations or immediate-release (crystalline) niacin preparations (see WARNINGS). Patients previously receiving niacin products other than NIASPAN should be started on NIASPAN with the recommended NIASPAN titration schedule, and the dose should subsequently be individualized based on patient response.

ADVICOR should be taken at bedtime, with a low-fat snack. ADVICOR tablets should be taken whole and should not be broken, crushed, or chewed before swallowing. The lowest initial ADVICOR dose is a single 500 mg/20 mg tablet once daily at bedtime. The dose of ADVICOR should not be increased by more than 500 mg daily (based on the NIASPAN component) every 4 weeks. The dose of ADVICOR should be individualized based on targeted goals for cholesterol and triglycerides, and on patient response. Doses of ADVICOR greater than 2000 mg/40 mg daily are not recommended. **If ADVICOR therapy is discontinued for an extended period (>7 days), reinstitution of therapy should begin with the lowest dose of ADVICOR.**

HOW SUPPLIED

ADVICOR is an unscored, capsule-shaped tablet containing either 500 or 1000 mg of niacin in an extended-release formulation and 20 mg of lovastatin in an immediate-release formulation. Tablets are color-coated and debossed with "KOS" on one side and the tablet strength code on the other side. ADVICOR 500 mg/20 mg tablets are light yellow, code "502". ADVICOR 1000 mg/20 mg tablets are dark pink/light purple, code "1002". Tablets are supplied in bottles of 90 tablets as shown below.

500 mg/20 mg tablets: bottles of 90 - NDC# 60598-006-90
1000 mg/20 mg tablets: bottles of 90 - NDC# 60598-008-90
Store at room temperature (20° to 25°C or 68° to 77°F).

Niaspan is a registered trademark of Kos Pharmaceuticals, Inc. and Mevacor is a registered trademark of Merck & Co., Inc.

REFERENCES

1. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; 285:2486-2497.
2. Downs JR, et al. *JAMA* 1998; 279:1615-1622.
3. Bradford RH, et al. *Arch Intern Med* 1991;151:43-49.
4. Bradford RH, et al. *Am J Cardiol* 1994; 74:667-673.
5. Manson JM, et al. *Reprod Toxicol* 1996; 10(6): 439-446.

Mfr. by:
Kos Pharmaceuticals, Inc.
Miami, FL 33131

400161/0604
Shown in Product Identification Guide, page 319

CARDIZEM® LA

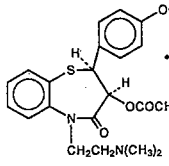
℞

[kăr-dĭ-zĕm]

(Diltiazem Hydrochloride)
Extended Release Tablets
℞ only
Once-a-Day Dosage

DESCRIPTION

Diltiazem hydrochloride is a calcium ion cellular influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2, 3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride, (+)-cis-. The structural formula is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol and chloroform. It has a molecular weight of 450.99. CARDIZEM® LA Tablets, for oral administration, are formulated as a once-a-day extended release tablet containing either 120 mg, 180 mg, 240 mg, 300 mg, 360 mg or 420 mg of diltiazem hydrochloride.

Also contains: Carnauba Wax NF, Colloidal Silicon Dioxide NF, Croscarmellose Sodium NF, Hydrogenated Vegetable Oil NF, Hypromellose USP, Magnesium Stearate NF, Microcrystalline Cellulose NF, Microcrystalline Wax NF, Pregelatinized Starch NF, Polyacrylate Dispersion 30%, Polyethylene Glycol NF, Polydextrose, Polysorbate NF, Povidone USP, Simethicone USP, Sodium Starch Glycolate NF, Sucrose Stearate, Talc USP, Titanium Dioxide USP.

CLINICAL PHARMACOLOGY

The therapeutic effects of diltiazem are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action

Hypertension. Diltiazem produces its antihypertensive effect primarily by relaxation of vascular smooth muscle and the resultant decrease in peripheral vascular resistance. The magnitude of blood pressure reduction is related to the degree of hypertension; thus hypertensive individuals experience an antihypertensive effect, whereas there is only a modest fall in blood pressure in normotensives.

Angina. Diltiazem has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal work loads. Diltiazem has been shown to be a potent dilator of coronary arteries, both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasms are inhibited by diltiazem.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissues. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem causes relaxation of coronary smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and non-ischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Pharmacokinetics and Metabolism

Diltiazem is well absorbed from the gastrointestinal tract and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous administration) of about 40%. Diltiazem undergoes extensive metabolism in which only 2% to 4% of the unchanged drug appears in the urine. Drugs which induce or inhibit hepatic microsomal enzymes may alter diltiazem disposition.

Total radioactivity measurement following short IV administration in healthy volunteers suggests the presence of other unidentified metabolites, which attain higher concentrations than those of diltiazem and are more slowly eliminated; half-life of total radioactivity is about 20 hours compared to 2 to 5 hours for diltiazem.

In vitro binding studies show diltiazem is 70% to 80% bound to plasma proteins. Competitive *in vitro* ligand binding studies have also shown diltiazem hydrochloride binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. The plasma elimination half-life following single or multiple drug administration is approximately 3.0 to 4.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent as a coronary vasodilator as diltiazem. Minimum therapeutic plasma diltiazem concentrations appear to be in the range of 50 to 200 ng/mL. There is a departure from linearity when dose strengths are increased; the half-life is slightly increased with dose. A study that compared patients with normal hepatic function to patients with cirrhosis found an increase in half-life and a 69% increase in bioavailability in the hepatically impaired patients. A single study in patients with severely impaired renal function showed no difference in the pharmacokinetic profile of diltiazem compared to patients with normal renal function.

CARDIZEM LA Tablets. A single 360 mg dose of CARDIZEM LA results in detectable plasma levels within 3 to 4 hours and peak plasma levels between 11 and 18 hours; absorption occurs throughout the dosing interval. The apparent elimination half-life for CARDIZEM LA Tablets after single or multiple dosing is 6 to 9 hours. When CARDIZEM LA Tablets were coadministered with a high fat content breakfast, diltiazem peak and systemic exposures were not affected indicating that the tablet can be administered without regard to food. As the dose of CARDIZEM LA Tablets is increased from 120 to 240 mg, area-under-the-curve increases 2.5-fold.

Pharmacodynamics and Clinical Studies

Like other calcium channel antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure in normotensive individuals and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. Such data has no predictive value with respect to effects in patients with poor ventricular function, and increased heart failure has been reported in patients with preexisting impairment of ventricular function. There are as yet few data on the interaction of diltiazem and beta-blockers in patients with poor ventricular function. Resting heart rate is usually slightly reduced by diltiazem. Diltiazem decreases vascular resistance, increases cardiac output (by increasing stroke volume), and produces a slight decrease or no change in heart rate.

During dynamic exercise, increases in diastolic pressure are inhibited, while maximum achievable systolic pressure is usually reduced. Chronic therapy with diltiazem produces no change or an increase in plasma catecholamines. No increased activity of the renin-angiotensin-aldosterone axis has been observed. Diltiazem reduces the renal and peripheral effects of angiotensin II. Hypertensive animal models respond to diltiazem with reductions in blood pressure and increased urinary output and natriuresis without a change in urinary sodium/potassium ratio.

Intravenous diltiazem hydrochloride in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods by approximately 20%. In a study involving single oral doses of 300 mg of diltiazem hydrochloride in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of diltiazem hydrochloride to patients in doses of up to 540 mg/day has resulted in small increases in PR interval, and on occasion produces abnormal prolongation (see WARNINGS).

Hypertension. In a randomized, double-blind, parallel-group, dose-response study involving 478 patients with essential hypertension, evening doses of CARDIZEM LA 120, 240, 360, and 540 mg were compared to placebo and to 360 mg administered in the morning. The mean reductions in diastolic blood pressure by ABPM at roughly 24 hours after the morning (4 AM - 8AM) or evening (6 PM -10 PM)

Continued on next page

Adverse Events Occurring at an Incidence of Greater Than 3% and Greater Than Placebo

Adverse Event	Azmacort Dose 200 mcg bid (n=57)	400 mcg bid (n=170)	800 mcg bid (n=57)	Placebo (n=167)
Sinusitis	5 (9%)	7 (4%)	1 (2%)	6 (4%)
Pharyngitis	4 (7%)	42 (25%)	10 (18%)	19 (11%)
Headache	4 (7%)	35 (21%)	7 (12%)	24 (14%)
Flu Syndrome	2 (4%)	8 (5%)	1 (2%)	5 (3%)
Back Pain	2 (4%)	3 (2%)	2 (4%)	3 (2%)

Adverse events that occurred at an incidence of 1-3% in the overall **Azmacort** Inhalation Aerosol treatment group and greater than placebo included:

Body as a whole: facial edema, pain, abdominal pain, photosensitivity
Digestive system: diarrhea, oral monilia, toothache, vomiting
Metabolic and Nutrition: weight gain
Musculoskeletal system: bursitis, myalgia, tenosynovitis
Nervous system: dry mouth
Organs of special sense: rash
Respiratory system: chest congestion, voice alteration
Urogenital system: cystitis, urinary tract infection, vaginal monilia

In older controlled clinical trials of steroid dependent asthmatics, urticaria was reported rarely. Anaphylaxis was not reported in these controlled trials. Typical steroid withdrawal effects including muscle aches, joint aches, and fatigue were noted in clinical trials when patients were transferred from oral steroid therapy to **Azmacort** Inhalation Aerosol. Easy bruisability was also noted in these trials. Hoarseness, dry throat, irritated throat, dry mouth, facial edema, increased wheezing, and cough have been reported. These adverse effects have generally been mild and transient. Cases of oral candidiasis occurring with clinical use have been reported. (See **WARNINGS**.)

Post Marketing: In addition to adverse events reported from clinical trials, the following events have been reported post marketing: anaphylaxis, cataracts, and glaucoma.

OVERDOSAGE

There are no data available on the effects of acute or chronic overdose. However, acute overdosing with **Azmacort** Inhalation Aerosol is unlikely in view of the total amount of active ingredient present and the route of administration. The maximum total daily dose (1600 mcg) has been well tolerated when administered as a single dose of 16 consecutive inhalations to adult asthmatics in a controlled clinical trial. Chronic overdosage may result in signs/symptoms of hypercorticoidism. (See **PRECAUTIONS**.) The risk of candidiasis could also be increased.

DOSAGE AND ADMINISTRATION

Adults: The usual recommended dosage is two inhalations (200 mcg) given three to four times a day or four inhalations (400 mcg) given twice daily. The maximal daily intake should not exceed 16 inhalations (1600 mcg) in adults. Higher initial doses (12 to 16 inhalations per day) may be considered in patients with more severe asthma.

Children 6 to 12 Years of Age: The usual recommended dosage is one or two inhalations (100 to 200 mcg) given three to four times a day or two to four inhalations (200 to 400 mcg) given twice daily. The maximal daily intake should not exceed 12 inhalations (1200 mcg) in children 6 to 12 years of age. Insufficient clinical data exist with respect to the safety and efficacy of the administration of **Azmacort** Inhalation Aerosol to children below the age of 6. The long-term effects of inhaled steroids, including **Azmacort** Inhalation Aerosol, on growth are still not fully known.

Rinsing the mouth after inhalation is advised.

Different considerations must be given to the following groups of patients in order to obtain the full therapeutic benefit of **Azmacort** Inhalation Aerosol:

Note: In all patients, it is desirable to titrate to the lowest effective dose once asthma stability has been achieved.

Patients Not Receiving Systemic Corticosteroids: Patients who require maintenance therapy of their asthma may benefit from treatment with **Azmacort** Inhalation Aerosol at the doses recommended above. In patients who respond to **Azmacort** Inhalation Aerosol, improvement in pulmonary function is usually apparent within one to two weeks after the initiation of therapy.

Patients Maintained on Systemic Corticosteroids: Clinical studies have shown that **Azmacort** Inhalation Aerosol may be effective in the management of asthmatics dependent or maintained on systemic corticosteroids and may permit replacement or significant reduction in the dosage of systemic corticosteroids.

The patient's asthma should be reasonably stable before treatment with **Azmacort** Inhalation Aerosol is started. Initially, **Azmacort** Inhalation Aerosol should be used concurrently with the patient's usual maintenance dose of systemic corticosteroid. After approximately one week, gradual withdrawal of the systemic corticosteroid is started by reducing the daily or alternate daily dose. Reductions may be made after an interval of one or two weeks, depending on the response of the patient. A slow rate of withdrawal is strongly recommended. Generally, these decrements should not exceed 2.5 mg of prednisone or its equivalent. During withdrawal, some patients may experience symptoms of systemic corticosteroid withdrawal, *e.g.*, joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement in pulmonary function. Such patients should be encouraged to continue with the inhaler but should be monitored for objective signs of adrenal insufficiency. If evidence of adrenal insufficiency occurs, the systemic corticosteroid doses should be increased temporarily and thereafter withdrawal should continue more slowly. Inhaled corticosteroids should be used with caution when used chronically in patients receiving prednisone regimens, either daily or alternate day. (See **WARNINGS**.)

During periods of stress or a severe asthma attack, transfer patients may require supplementary treatment with systemic corticosteroids.

Directions for Use: An illustrated leaflet of patient instructions for proper use accompanies each package of **Azmacort** Inhalation Aerosol.

HOW SUPPLIED

Azmacort Inhalation Aerosol contains 60 mg triamcinolone acetonide in a 20 gram package which delivers at least 240 actuations. It is supplied with a white plastic actuator, a white plastic spacer-mouthpiece and patient's leaflet of instructions: box of one. NDC 60598-061-60. Each actuation delivers 200 mcg triamcinolone acetonide from the valve and 100 mcg from the spacer-mouthpiece under defined *in vitro* test conditions.

Avoid spraying in eyes.

For best results, the canister should be at room temperature before use.

Shake well before using.

CONTENTS UNDER PRESSURE. Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw canister into fire or incinerator. Keep out of reach of children unless otherwise prescribed. Store at Controlled Room Temperature 20 to 25°C (68 to 77°F) [see USP].

Note: The indented statement below is required by the Federal government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFCs):

WARNING: Contains CFC-12, a substance which harms public health and the environment by destroying ozone in the upper atmosphere.

A notice similar to the above WARNING has been placed in the "Information For The Patient" portion of this package insert under the Environmental Protection Agency's (EPA's) regulations. The patient's warning states that the patient should consult his or her physician if there are questions about alternatives.

Manufactured for: Kos Pharmaceuticals, Inc.
Cranbury, NJ 08512
400201/0604
Rev. June 2004
50072141

Shown in Product Identification Guide, page 319

NIASPAN®

℞

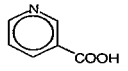
[niă-span]

(niacin extended-release tablets)

℞ Only

DESCRIPTION

NIASPAN® (niacin extended-release tablets), contain niacin, a B-complex vitamin and antihyperlipidemic agent. Niacin (nicotinic acid, or 3-pyridinecarboxylic acid) is a white, crystalline powder, very soluble in water, with the following structural formula:



$C_6H_5NO_2$ M.W. = 123.11

NIASPAN is an unscored, off-white tablet for oral administration that contains no color additives and is available in three tablet strengths containing 500, 750, and 1000mg niacin. NIASPAN tablets also contain the inactive ingredients hypromellose, povidone, and stearic acid.

CLINICAL PHARMACOLOGY

Niacin functions in the body after conversion to nicotinamide adenine dinucleotide (NAD) in the NAD coenzyme system. Niacin (but not nicotinamide) in gram doses reduces total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG), and increases high-density lipoprotein cholesterol (HDL-C). The magnitude of the individual lipid and lipoprotein responses may be influenced by the severity and type of underlying lipid abnormality. The increase in total HDL-C is associated with an increase in apolipoprotein A-I (Apo A-I) and a shift in the distribution of HDL subfractions. These shifts include an increase in the HDL_2:HDL_3 ratio, and an elevation in lipoprotein A-I (Lp A-I, an HDL particle containing only Apo A-I). Niacin treatment also decreases serum levels of apolipoprotein B-100 (Apo B), the major protein component of the very low-density lipoprotein (VLDL) and LDL fractions, and of Lp(a), a variant form of LDL independently associated with coronary risk.[1] In addition, preliminary reports suggest that niacin causes favorable LDL particle size transformations, although the clinical relevance of this effect requires further investigation. The effect of niacin-induced changes in lipids/lipoproteins on cardiovascular morbidity or mortality in individuals without pre-existing coronary disease has not been established.

A variety of clinical studies have demonstrated that elevated levels of TC, LDL-C, and Apo B promote human atherosclerosis. Similarly, decreased levels of HDL-C are associated with the development of atherosclerosis. Epidemiological investigations have established that cardiovascular morbidity and mortality vary directly with the level of TC and LDL-C, and inversely with the level of HDL-C.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate-density lipoprotein (IDL), and their remnants, can also promote atherosclerosis. Elevated plasma TG are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease (CHD). As such total plasma TG have not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL-C or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

Mechanism of Action

The mechanism by which niacin alters lipid profiles has not been well defined. It may involve several actions including partial inhibition of release of free fatty acids from adipose tissue, and increased lipoprotein lipase activity, which may increase the rate of chylomicron triglyceride removal from plasma. Niacin decreases the rate of hepatic synthesis of VLDL and LDL, and does not appear to affect fecal excretion of fats, sterols, or bile acids.

Pharmacokinetics/Metabolism

Absorption

Niacin is rapidly and extensively absorbed (at least 60 to 76% of dose) when administered orally. To maximize bioavailability and reduce the risk of gastrointestinal (GI) upset, administration of NIASPAN with a low-fat meal or snack is recommended.

Single-dose bioavailability studies have demonstrated that NIASPAN tablet strengths are not interchangeable.

Distribution

Studies using radiolabeled niacin in mice show that niacin and its metabolites concentrate in the liver, kidney and adipose tissue.

Metabolism

The pharmacokinetic profile of niacin is complicated due to rapid and extensive first-pass metabolism, which is species and dose-rate specific. In humans, one pathway is through a simple conjugation step with glycine to form nicotinuric acid (NUA). NUA is then excreted in the urine, although there may be a small amount of reversible metabolism back to niacin. The other pathway results in the formation of nicotinamide adenine dinucleotide (NAD). It is unclear whether nicotinamide is formed as a precursor to, or following the synthesis of, NAD. Nicotinamide is further metabolized to at least N-methylnicotinamide (MNA) and nicotinamide-N-oxide (NNO). MNA is further metabolized to two other compounds, N-methyl-2-pyridone-5-carboxamide (2PY) and N-methyl-4-pyridone-5-carboxamide (4PY). The formation of 2PY appears to predominate over 4PY in humans. At the doses used to treat hyperlipidemia, these metabolic pathways are saturable, which explains the nonlinear relationship between niacin dose and plasma concentrations following multiple-dose NIASPAN administration (Table 1). Nicotinamide does not have hypolipidemic activity; the activity of the other metabolites is unknown.

Table 1. Mean Steady-State Pharmacokinetic Parameters for Plasma Niacin

NIASPAN dose/day	NIASPAN given as	Niacin Peak Concentration (µg/mL)	Niacin Time to Peak (hrs)
1000mg	2×500mg	0.6	5
1500mg	2×750mg	4.9	4
2000mg	2×1000mg	15.5	5

Elimination

Niacin and its metabolites are rapidly eliminated in the urine. Following single and multiple doses, approximately 60 to 76% of the niacin dose administered as NIASPAN was recovered in urine as niacin and metabolites; up to 12% was recovered as unchanged niacin after multiple dosing. The ratio of metabolites recovered in the urine was dependent on the dose administered.

Special Populations

Hepatic

No studies have been performed. NIASPAN should be used with caution in patients with a past history of liver disease, who consume substantial quantities of alcohol, or have unexplained transaminase elevations. NIASPAN is contraindicated in patients with active liver disease (see **WARNINGS, Liver Dysfunction**).

Continued on next page

Niaspan—Cont.

Renal

There are no data in this population. NIASPAN should be used with caution in patients with renal disease (see **PRECAUTIONS**).

Gender

Steady-state plasma concentrations of niacin and metabolites after administration of NIASPAN are generally higher in women than in men, with the magnitude of the difference varying with dose and metabolite. Recovery of niacin and metabolites in urine, however, is generally similar for men and women, indicating that absorption is similar for both genders. The gender differences observed in plasma levels of niacin and its metabolites may be due to gender-specific differences in metabolic rate or volume of distribution. Data from the clinical trials suggest that women have a greater hypolipidemic response than men at equivalent doses of NIASPAN.

Niacin Clinical Studies

The role of LDL-C in atherogenesis is supported by pathological observations, clinical studies, and many animal experiments. Observational epidemiological studies have clearly established that high TC or LDL-C and low HDL-C are risk factors for CHD. Additionally, elevated levels of Lp(a) have been shown to be independently associated with CHD risk.[1] The efficacy of niacin in improving lipoprotein lipid profiles, either alone or in combination with other lipid-altering drugs, as an adjunct to diet therapy in the treatment of hyperlipoproteinemia has been well documented.

Niacin's ability to reduce mortality and the risk of definite, nonfatal myocardial infarction (MI) has also been assessed in long-term studies. The Coronary Drug Project,[2] completed in 1975, was designed to assess the safety and efficacy of niacin and other lipid-altering drugs in men 30 to 64 years old with a history of MI. Over an observation period of 5 years, niacin treatment was associated with a statistically significant reduction in nonfatal, recurrent MI. The incidence of definite, nonfatal MI was 8.9% for the 1,119 patients randomized to nicotinic acid versus 12.2% for the 2,789 patients who received placebo ($p<0.004$). Total mortality was similar in the two groups at 5 years (24.4% with nicotinic acid versus 25.4% with placebo; p=N.S.). At the time of a 15-year follow-up, there were 11% (69) fewer deaths in the niacin group compared to the placebo cohort (52.0% versus 58.2%; p=0.0004).[3] However, mortality at 15 years was not an original endpoint of the Coronary Drug Project. In addition, patients had not received niacin for approximately 9 years, and confounding variables such as concomitant medication use and medical or surgical treatments were not controlled.

The Cholesterol-Lowering Atherosclerosis Study (CLAS) was a randomized, placebo-controlled, angiographic trial testing combined colestipol and niacin therapy in 162 nonsmoking males with previous coronary bypass surgery.[4] The primary, per-subject cardiac endpoint was global coronary artery change score. After 2 years, 61% of patients in the placebo cohort showed disease progression by global change score (n=82), compared with only 38.8% of drug-treated subjects (n=80), when both native arteries and grafts were considered ($p<0.005$); disease regression also occurred more frequently in the drug-treated group (16.2% versus 2.4%; p=0.002). In a follow-up to this trial in a subgroup of 103 patients treated for 4 years, again, significantly fewer patients in the drug-treated group demonstrated progression than in the placebo cohort (48% versus 85%, respectively; $p<0.0001$).[5]

The Familial Atherosclerosis Treatment Study (FATS) in 146 men ages 62 and younger with Apo B levels ≥125 mg/dL, established coronary artery disease, and family histories of vascular disease, assessed change in severity of disease in the proximal coronary arteries by quantitative arteriography.[6] Patients were given dietary counseling and randomized to treatment with either conventional therapy with double placebo (or placebo plus colestipol if the LDL-C was elevated); lovastatin plus colestipol; or niacin plus colestipol. In the conventional therapy group, 46% of patients had disease progression (and no regression) in at least one of nine proximal coronary segments; regression was the only change in 11%. In contrast, progression (as the only change) was seen in only 25% in the niacin plus colestipol group, while regression was observed in 39%. Though not an original endpoint of the trial, clinical events (death, MI, or revascularization for worsening angina) occurred in 10 of 52 patients who received conventional therapy, compared with 2 of 48 who received niacin plus colestipol.

The Harvard Atherosclerosis Reversibility Project (HARP) was a randomized placebo-controlled, 2.5-year study of the effect of a stepped-care antihyperlipidemic drug regimen on 91 patients (80 men and 11 women) with CHD and average baseline TC levels less than 250 mg/dL and ratios of TC to HDL-C greater than 4.0.[7] Drug treatment consisted of an HMG-CoA reductase inhibitor administered alone as initial therapy followed by addition of varying dosages of either a slow-release nicotinic acid, cholestyramine, or gemfibrozil. Addition of nicotinic acid to the HMG-CoA reductase inhibitor resulted in further statistically significant mean reductions in TC, LDL-C, and TG, as well as a further increase in HDL-C in a majority of patients (40 of 44 patients). The ratios of TC to HDL-C and LDL-C to HDL-C were also significantly reduced by this combination drug regimen (see **WARNINGS**, ***Skeletal Muscle***).

Table 2. Lipid Response to NIASPAN Therapy

Treatment	n	Mean Percent Change from Baseline to Week 16*							
		TC	LDL-C	HDL-C	TC/HDL-C	TG	Lp(a)	Apo B	Apo A-1
NIASPAN 1000mg qhs	41	−3	−5	+18	−17	−21	−13	−6	+9
NIASPAN 2000mg qhs	41	−10	−14	+22	−25	−28	−27	−16	+8
Placebo	40	0	−1	+4	−3	0	0	+1	+3
NIASPAN 1500mg qhs	76	−8	−12	+20	−20	−13	−15	−12	+8
Placebo	73	+2	+1	+2	+1	+12	+2	+1	+2

n = number of patients at baseline;
* Mean percent change from baseline for all NIASPAN doses was significantly different ($p<0.05$) from placebo for all lipid parameters shown except Apo A-1 at 2000mg.

Table 3. Lipid Response in Dose-Escalation Study

Treatment	n	Mean Percent Change from Baseline*							
		TC	LDL-C	HDL-C	TC/HDL-C	TG	Lp(a)	Apo B	Apo A-1
Placebo‡	44	−2	−1	+5	−7	−6	−5	−2	+4
NIASPAN	87								
500mg qhs		−2	−3	+10	−10	−5	−3	−2	+5
1000mg qhs		−5	−9	+15	−17	−11	−12	−7	+8
1500mg qhs		−11	−14	+22	−26	−28	−20	−15	+10
2000mg qhs		−12	−17	+26	−29	−35	−24	−16	+12

n = number of patients enrolled;
‡ Placebo data shown are after 24 weeks of placebo treatment.
* For all NIASPAN doses except 500mg, mean percent change from baseline was significantly different ($p<0.05$) from placebo for all lipid parameters shown except Lp(a) and Apo A-1 which were significantly different from placebo starting with 1500mg and 2000mg, respectively.

Table 4. Selected Lipid Response to NIASPAN in Placebo-Controlled Clinical Studies*

NIASPAN Dose	n	Mean Baseline and Median Percent Change from Baseline (25th, 75th Percentiles)		
		LDL-C	HDL-C	TG
1000mg qhs	104			
Baseline (mg/dL)		218	45	172
Percent Change		−7 (−15, 0)	+14 (+7,+23)	−16 (−34,+3)
1500mg qhs	120			
Baseline (mg/dL)		212	46	171
Percent Change		−13 (−21,−4)	+19 (+9,+31)	−25 (−45,−2)
2000mg qhs	85			
Baseline (mg/dL)		220	44	160
Percent Change		−16 (−26,−7)	+22 (+15,+34)	−38 (−52,−14)

* Represents pooled analyses of results; minimum duration on therapy at each dose was 4 weeks.

Table 5. Effect of Gender on NIASPAN Dose Response

NIASPAN Dose	n (M/F)	Mean Percent Change from Baseline							
		LDL-C		HDL-C		TG		Apo B	
		M	F	M	F	M	F	M	F
500mg qhs	50/37	−2	−5	+11	+8	−3	−9	−1	−5
1000mg qhs	76/52	−6*	−11*	+14	+20	−10	−20	−5*	−10*
1500mg qhs	104/59	−12	−16	+19	+24	−17	−28	−13	−15
2000mg qhs	75/53	−15	−18	+23	+26	−30	−36	−16	−16

n = number of male/female patients enrolled.
* Percent change significantly different between genders ($p<0.05$).

Table 6. Lipid Response to NIASPAN in Patients with Low HDL-C

	n	Mean Baseline and Mean Percent Change from Baseline								
		TC	LDL-C	HDL-C	TC/HDL-C	TG	Lp(a)†	Apo B†	Apo A-I†	Lp A-I‡
Baseline (mg/dL)	88	190	120	31	6	194	8	106	105	32
Week 19 (% Change)	71	−3	0	+26	−22	−30	−20	−9	+11	+20

n = number of patients enrolled
* Mean percent change from baseline was significantly different ($p<0.05$) for all lipid parameters shown except LDL-C.
†n=72 at baseline and 69 at week 19.
‡n=30 at baseline and week 19.

NIASPAN Clinical Studies

Placebo-Controlled Clinical Studies in Patients with Primary Hypercholesterolemia and Mixed Dyslipidemia: In two randomized, double-blind, parallel, multi-center, placebo-controlled trials, NIASPAN dosed at 1000, 1500 or 2000mg daily at bedtime with a low-fat snack for 16 weeks (including 4 weeks of dose escalation) favorably altered lipid profiles compared to placebo (Table 2). Women appeared to have a greater response than men at each NIASPAN dose level (see *Gender Effect*, below).

[See table 2 above]

In a double-blind, multi-center, forced dose-escalation study, monthly 500mg increases in NIASPAN dose resulted in incremental reductions of approximately 5% in LDL-C and Apo B levels in the daily dose range of 500mg through 2000mg (Table 3). Women again tended to have a greater response to NIASPAN than men (see *Gender Effect*, below).

[See table 3 above]

Pooled results for major lipids from these three placebo-controlled studies are shown below (Table 4).

[See table 4 above]

Gender Effect: Combined data from the three placebo-controlled NIASPAN studies in patients with primary hypercholesterolemia and mixed dyslipidemia suggest that, at each NIASPAN dose level studied, changes in lipid concentrations are greater for women than for men (Table 5).

[See table 5 above]

Other Patient Populations: In a double-blind, multi-center, 19-week study the lipid-altering effects of NIASPAN (forced titration to 2000mg qhs) were compared to baseline in patients whose primary lipid abnormality was a low level of HDL-C (HDL-C ≤40 mg/dL, TG ≤400 mg/dL, and LDL-C ≤160, or <130 mg/dL in the presence of CHD). Results are shown below (Table 6).

[See table 6 above]

At NIASPAN 2000 mg/day, median changes from baseline (25th, 75th percentiles) for LDL-C, HDL-C, and TG were −3% (−14, +12%), +27% (+13, +38%), and −33% (−50, −19%), respectively.

Combination NIASPAN and Lovastatin Study: In a multicenter, randomized, double-blind, parallel, 28-week study, a combination tablet of NIASPAN and lovastatin was compared to each individual component in patients with Type IIa and IIb hyperlipidemia. Using a forced dose-escalation study design, patients received each dose for at least 4 weeks. Patients randomized to treatment with the combination tablet of NIASPAN and lovastatin initially received 500mg/20mg (expressed as mg of niacin/mg of lovastatin) once daily before bedtime. The dose was increased by 500mg at 4-week intervals (based on the NIASPAN component) to a maximum dose of 1000mg/20mg or one-half of the patients and 2000mg/40mg in the other half. The NIASPAN monotherapy group underwent a similar titration from 500mg to 2000mg. The patients randomized to lovastatin monotherapy received 20mg for 12 weeks titrated to 40mg for up to 16 weeks. Up to a third of the patients randomized to the combination tablet of NIASPAN and lovastatin or NIASPAN monotherapy discontinued prior to Week 28. Results from this study showed that combination therapy decreased LDL-C, TG and Lp(a), and increased HDL-C in a dose-dependent fashion (Tables 7, 8, 9, and 10). Results from this study for LDL-C mean percent change from baseline (the primary efficacy variable) showed that:

1) LDL-lowering with the combination tablet of NIASPAN and lovastatin was significantly greater than that achieved with lovastatin 40mg only after 28 weeks of titration to a dose of 2000mg/40mg ($p<0.0001$)
2) The combination tablet of NIASPAN and lovastatin at doses of 1000mg/20mg or higher achieved greater LDL-lowering NIASPAN ($p<0.0001$)

The LDL-C results are sumarized in Table 7.
[See table 7 above]

Combination therapy achieved significantly greater HDL-raising compared to lovastatin and NIASPAN monotherapy at all doses (Table 8).
[See table 8 above]

In addition, combination therapy achieved significantly greater TG-lowering at doses of 1000mg/20mg or greater compared to lovastatin and NIASPAN monotherapy (Table 9).
[See table 9 at right]

The Lp(a)-lowering effects of combination therapy and NIASPAN monotherapy were similar, and both were superior to lovastatin (Table 10). The independent effect of lowering Lp(a) with NIASPAN or combination therapy on the risk of coronary and cardiovascular morbidity and mortality has not been determined.
[See table 10 at right]

INDICATIONS AND USAGE

Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Niacin therapy is indicated as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate (see also the NCEP treatment guideline;[8] Table 11). Prior to initiating therapy with niacin, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile obtained to measure TC, HDL-C, and TG.

1. NIASPAN is indicated as an adjunct to diet for reduction of elevated TC, LDL-C, Apo B and TG levels, and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Frederickson Types IIa and IIb; Table 12), when the response to an appropriate diet has been inadequate.
2. NIASPAN in combination with lovastatin is indicated for the treatment of primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Frederickson Types IIa and IIb; Table 12) in:
   - Patients treated with lovastatin who require further TG-lowering or HDL-raising who may benefit from having niacin added to their regimen
   - Patients treated with niacin who require further LDL-lowering who may benefit from having lovastatin added to their regimen

   Combination therapy is not indicated as initial therapy. (See **DOSAGE AND ADMINISTRATION**.)
3. In patients with a history of myocardial infarction and hypercholesterolemia, niacin is indicated to reduce the risk of recurrent nonfatal myocardial infarction.
4. In patients with a history of coronary artery disease (CAD) and hypercholesterolemia, niacin, in combination with a bile acid binding resin, is indicated to slow progression or promote regression of atherosclerotic disease.
5. NIASPAN in combination with a bile acid binding resin is indicated as an adjunct to diet for reduction of elevated TC and LDL-C levels in adult patients with primary hypercholesterolemia (Type IIa; Table 12), when the response to an appropriate diet, or diet plus monotherapy, has been inadequate.
6. Niacin is also indicated as adjunctive therapy for treatment of adult patients with very high serum triglyceride levels (Types IV and V hyperlipidemia; Table 12) who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them. Such patients typically have serum TG levels over 2000 mg/dL and have elevations of VLDL-C as well as fasting chylomicrons (Type V hyperlipidemia; Table 12). Patients who consistently have total serum or plasma TG below 1000 mg/dL are unlikely to develop pancreatitis. Therapy with niacin may be considered for those patients with TG elevations between 1000 and 2000 mg/dL who have a history of pancreatitis or of recurrent abdominal pain typical of pancreatitis. Some Type IV patients with TG under 1000 mg/dL may, through dietary or alcohol indiscretion, convert to a Type V pattern with massive TG elevations accompanying fasting chylomicronemia, but the influence of niacin therapy on risk of pancreatitis in such situations has not been adequately studied. Drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma TG, but who have normal levels of VLDL-C. Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV, and V hyperlipoproteinemia.[9]

[See table 11 above]

Table 7. LDL-C mean percent change from baseline

Week	Combination tablet of NIASPAN and lovastatin			NIASPAN			Lovastatin		
	n*	Dose (mg/mg)	LDL	n*	Dose (mg)	LDL	n*	Dose (mg)	LDL
Baseline	57	-	190.9 mg/dL	61	-	189.7 mg/dL	61	-	185.6 mg/dL
12	47	1000/20	−30%	46	1000	−3%	56	20	−29%
16	45	1000/40	−36%	44	1000	−6%	56	40	−31%
20	42	1500/40	−37%	43	1500	−12%	54	40	−34%
28	42	2000/40	−42%	41	2000	−14%	53	40	−32%

*n = number of patients remaining in trial at each time point.

Table 8. HDL-C mean percent change from baseline

Week	Combination tablet of NIASPAN and lovastatin			NIASPAN			Lovastatin		
	n*	Dose (mg/mg)	HDL	n*	Dose (mg)	HDL	n*	Dose (mg)	HDL
Baseline	57	-	45 mg/dL	61	-	47 mg/dL	61	-	43 mg/dL
12	47	1000/20	+20%	46	1000	+14%	56	20	+3%
16	45	1000/40	+20%	44	1000	+15%	56	40	+5%
20	42	1500/40	+27%	43	1500	+22%	54	40	+6%
28	42	2000/40	+30%	41	2000	+24%	53	40	+6%

*n = number of patients remaining in trial at each time point.

Table 9. TG median percent change from baseline

Week	Combination tablet of NIASPAN and lovastatin			NIASPAN			Lovastatin		
	n*	Dose (mg/mg)	TG	n*	Dose (mg)	TG	n*	Dose (mg)	TG
Baseline	57	-	174 mg/dL	61	-	186 mg/dL	61	-	171 mg/dL
12	47	1000/20	−32%	46	1000	−22%	56	20	−20%
16	45	1000/40	−39%	44	1000	−23%	56	40	−17%
20	42	1500/40	−44%	43	1500	−31%	54	40	−21%
28	42	2000/40	−44%	41	2000	−31%	53	40	−20%

*n = number of patients remaining in trial at each time point.

Table 10. Lp(a) median percent change from baseline

Week	Combination tablet of NIASPAN and lovastatin			NIASPAN			Lovastatin		
	n*	Dose (mg/mg)	Lp(a)	n*	Dose (mg)	Lp(a)	n*	Dose (mg)	Lp(a)
Baseline	57	-	34 mg/dL	61	-	41 mg/dL	60	-	42 mg/dL
12	47	1000/20	−9%	46	1000	−8%	55	20	+8%
16	45	1000/40	−9%	44	1000	−12%	55	40	+8%
20	42	1500/40	−17%	43	1500	−22%	53	40	+6%
28	42	2000/40	−22%	41	2000	−32%	52	40	0%

*n = number of patients remaining in trial at each time point.

Table 11. NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD† or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100–129: drug optional)††
2+ Risk factors (10-year risk ≤20%)	<130	≥130	10-year risk 10%–20%: ≥130 10-year risk <10%: ≥160
0–1 Risk factor†††	<160	≥160	≥190 (160–189: LDL-lowering drug optional)

†CHD, coronary heart disease
††Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.
†††Almost all people with 0–1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0–1 risk factor is not necessary.

Continued on next page

Niaspan—Cont.

After the LDL-C goal has been achieved, if the TG is still ≥200 mg/dL, non-HDL-C (TC minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk therapy.

Table 12. Classification of Hyperlipoproteinemias

Type	Lipoproteins Elevated	Lipid Elevations Major	Minor
I (rare)	chylomicrons	TG	↑→TC
IIa	LDL	TC	-
IIb	LDL, VLDL	TC	TG
III (rare)	IDL	TC/TG	-
IV	VLDL	TG	↑→TC
V (rare)	chylomicrons, VLDL	TG	↑→TC

TC = total cholesterol; TG = triglycerides; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein; IDL = intermediate-density lipoprotein
↑→ = increased or no change

CONTRAINDICATIONS

NIASPAN is contraindicated in patients with a known hypersensitivity to niacin or any component of this medication, significant or unexplained hepatic dysfunction, active peptic ulcer disease, or arterial bleeding.

WARNINGS

NIASPAN preparations should not be substituted for equivalent doses of immediate-release (crystalline) niacin. For patients switching from immediate-release niacin to NIASPAN, therapy with NIASPAN should be initiated with low doses (i.e., 500 mg qhs) and the NIASPAN dose should then be titrated to the desired therapeutic response (see DOSAGE AND ADMINISTRATION).

Liver Dysfunction

Cases of severe hepatic toxicity, including fulminant hepatic necrosis, have occurred in patients who have substituted sustained-release (modified-release, timed-release) niacin products for immediate-release (crystalline) niacin at equivalent doses.

NIASPAN should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of NIASPAN.

Niacin preparations, like some other lipid-lowering therapies, have been associated with abnormal liver tests. In three placebo-controlled clinical trials involving titration to final daily NIASPAN doses ranging from 500 to 3000mg, 245 patients received NIASPAN for a mean duration of 17 weeks. No patient with normal serum transaminase levels (AST, ALT) at baseline experienced elevations to more than 3 times the upper limit of normal (ULN) during treatment with NIASPAN. In these studies, fewer than 1% (2/245) of NIASPAN patients discontinued due to transaminase elevations greater than 2 times the ULN.

In three safety and efficacy studies with a combination tablet of NIASPAN and lovastatin involving titration to final daily doses (expressed as mg of Niacin/mg of lovastatin) 500mg/10mg to 2500mg/40mg, ten of 1028 patients (1.0%) experienced reversible elevations in AST/ALT to more than 3 times the upper limit of normal (ULN). Three of ten elevations occurred at doses outside the recommended dosing limit of 2000mg/40mg; no patient receiving 1000mg/20mg had 3-fold elevations in AST/ALT.

In the placebo-controlled clinical trials and the long-term extension study, elevations in transaminases did not appear to be related to treatment duration; elevations in AST levels did appear to be dose related. Transaminase elevations were reversible upon discontinuation of NIASPAN.

Liver tests should be performed on all patients during therapy with NIASPAN. Serum transaminase levels, including AST and ALT (SGOT and SGPT), should be monitored before treatment begins, every 6 weeks to 12 weeks for the first year, and periodically thereafter (e.g., at approximately 6-month intervals). Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times the ULN and are persistent, or if they are associated with symptoms of nausea, fever, and/or malaise, the drug should be discontinued.

Skeletal Muscle

Rare cases of rhabdomyolysis have been associated with concomitant administration of lipid-altering doses (≥1 g/day) of niacin and HMG-CoA reductase inhibitors. In clinical studies with a combination tablet of NIASPAN and lovastatin, no cases of rhabdomyolysis and one suspected case of myopathy have been reported in 1079 patients who were treated with doses up to 2000mg of NIASPAN and 40mg of lovastatin daily for periods up to 2 years. **Physicians contemplating combined therapy with HMG-CoA reductase inhibitors and NIASPAN should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug.** Periodic serum creatine phosphokinase (CPK) and potassium determinations should be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

PRECAUTIONS

General

Before instituting therapy with NIASPAN, an attempt should be made to control hyperlipidemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see **INDICATIONS AND USAGE**).

Patients with a past history of jaundice, hepatobiliary disease, or peptic ulcer should be observed closely during NIASPAN therapy. Frequent monitoring of liver function tests and blood glucose should be performed to ascertain that the drug is producing no adverse effects on these organ systems. Diabetic patients may experience a dose-related rise in glucose intolerance, the clinical significance of which is unclear. Diabetic or potentially diabetic patients should be observed closely. Adjustment of diet and/or hypoglycemic therapy may be necessary.

Caution should also be used when NIASPAN is used in patients with unstable angina or in the acute phase of an MI, particularly when such patients are also receiving vasoactive drugs such as nitrates, calcium channel blockers, or adrenergic blocking agents.

Elevated uric acid levels have occurred with niacin therapy, therefore use with caution in patients predisposed to gout.

NIASPAN has been associated with small but statistically significant dose-related reductions in platelet count (mean of -11% with 2000mg). In addition, NIASPAN has been associated with small but statistically significant increases in prothrombin time (mean of approximately +4%); accordingly, patients undergoing surgery should be carefully evaluated. Caution should be observed when NIASPAN is administered concomitantly with anticoagulants; prothrombin time and platelet counts should be monitored closely in such patients.

In placebo-controlled trials, NIASPAN has been associated with small but statistically significant, dose-related reductions in phosphorus levels (mean of −13% with 2000mg). Although these reductions were transient, phosphorus levels should be monitored periodically in patients at risk for hypophosphatemia.

Niacin is rapidly metabolized by the liver, and excreted through the kidneys. NIASPAN is contraindicated in patients with significant or unexplained hepatic dysfunction (see **CONTRAINDICATIONS** and **WARNINGS**) and should be used with caution in patients with renal dysfunction.

Information for Patients

Patients should be advised:

— to take NIASPAN at bedtime, after a low-fat snack. Administration on an empty stomach is not recommended;
— to carefully follow the prescribed dosing regimen, including the recommended titration schedule, in order to minimize side effects (see **DOSAGE AND ADMINISTRATION**);
— that flushing is a common side effect of niacin therapy that usually subsides after several weeks of consistent niacin use. Flushing may vary in severity, may last for several hours after dosing, and will, by taking NIASPAN at bedtime, most likely occur during sleep; however, if awakened by flushing at night, to get up slowly, especially if feeling dizzy, feeling faint, or taking blood pressure medications;
— that taking aspirin (approximately 30 minutes before taking NIASPAN) or a non-steroidal anti-inflammatory drug (e.g., ibuprofen) may minimize flushing;
— to avoid ingestion of alcohol or hot drinks around the time of NIASPAN administration, to minimize flushing;
— that if NIASPAN therapy is discontinued for an extended length of time, their physician should be contacted prior to re-starting therapy; re-titration is recommended (see **DOSAGE AND ADMINISTRATION**; Table 14);
— to notify their physician if they are taking vitamins or other nutritional supplements containing niacin or related compounds such as nicotinamide (see **Drug Interactions**);
— to notify their physician if symptoms of dizziness occur;
— if diabetic, to notify their physician of changes in blood glucose;
— that NIASPAN tablets should not be broken, crushed or chewed, but should be swallowed whole.

Drug Interactions

HMG-CoA Reductase Inhibitors: See **WARNINGS**, ***Skeletal Muscle***.

Antihypertensive Therapy: Niacin may potentiate the effects of ganglionic blocking agents and vasoactive drugs resulting in postural hypotension.

Aspirin: Concomitant aspirin may decrease the metabolic clearance of nicotinic acid. The clinical relevance of this finding is unclear.

Bile Acid Sequestrants: An *in vitro* study was carried out investigating the niacin-binding capacity of colestipol and cholestyramine. About 98% of available niacin was bound to colestipol, with 10 to 30% binding to cholestyramine. These results suggest that 4 to 6 hours, or as great an interval as possible, should elapse between the ingestion of bile acid-binding resins and the administration of NIASPAN.

Other: Concomitant alcohol or hot drinks may increase the side effects of flushing and pruritus and should be avoided around the time of NIASPAN ingestion. Vitamins or other nutritional supplements containing large doses of niacin or related compounds such as nicotinamide may potentiate the adverse effects of NIASPAN.

Drug/Laboratory Test Interactions

Niacin may produce false elevations in some fluorometric determinations of plasma or urinary catecholamines. Niacin may also give false-positive reactions with cupric sulfate solution (Benedict's reagent) in urine glucose tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Niacin administered to mice for a lifetime as a 1% solution in drinking water was not carcinogenic. The mice in this study received approximately 6 to 8 times a human dose of 3000 mg/day as determined on a mg/m^2 basis. Niacin was negative for mutagenicity in the Ames test. No studies on impairment of fertility have been performed. No studies have been conducted with NIASPAN regarding carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy

Pregnancy Category C.

Animal reproduction studies have not been conducted with niacin or with NIASPAN. It is also not known whether niacin at doses typically used for lipid disorders can cause fetal harm when administered to pregnant women or whether it can affect reproductive capacity. If a woman receiving niacin for primary hypercholesterolemia (Types IIa or IIb) becomes pregnant, the drug should be discontinued. If a woman being treated with niacin for hypertriglyceridemia (Types IV or V) conceives, the benefits and risks of continued therapy should be assessed on an individual basis.

Nursing Mothers

Niacin has been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from lipid-altering doses of nicotinic acid, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. No studies have been conducted with NIASPAN in nursing mothers.

Pediatric Use

Safety and effectiveness of niacin therapy in pediatric patients (≤16 years) have not been established. No studies in patients under 21 years of age have been conducted with NIASPAN.

Geriatric Use

Of 979 patients in clinical studies of NIASPAN, 21% of the patients were age 65 and over. No overall differences in safety and effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

NIASPAN is generally well tolerated; adverse reactions have been mild and transient. In the placebo-controlled clinical trials, flushing episodes (i.e., warmth, redness, itching and/or tingling) were the most common treatment-emergent adverse events (reported by as many as 88% of patients) for NIASPAN. Spontaneous reports suggest that flushing may also be accompanied by symptoms of dizziness, tachycardia, palpitations, shortness of breath, sweating, chills, and/or edema, which in rare cases may lead to syncope. In pivotal studies, fewer that 6% (14/245) of NIASPAN patients discontinued due to flushing. In comparisons of immediate-release (IR) niacin and NIASPAN, although the proportion of patients who flushed was similar, fewer flushing episodes were reported by patients who received NIASPAN. Following 4 weeks of maintenance therapy at daily doses of 1500mg, the incidence of flushing over the 4-week period averaged 8.56 events per patient for IR niacin versus 1.88 following NIASPAN.

Other adverse events occurring in 5% or greater of patients treated with NIASPAN, at least remotely related to NIASPAN, are shown in Table 13 below.

[See table 13 at top of next page]

The following adverse events have also been reported with NIASPAN® or other niacin products, either during clinical trials or in routine patient management.

Body as a Whole: generalized edema; face edema; peripheral edema, asthenia, chills

Cardiovascular: atrial fibrillation, and other cardiac arrhythmias; tachycardia, palpitations; orthostasis; syncope; hypotension

Eye: toxic amblyopia, crystoid macular edema

Gastrointestinal: activation of peptic ulcers and peptic ulceration; jaundice; eructation; flatulence

Metabolic: decreased glucose tolerance; gout

Musculoskeletal: myalgia; myasthenia

Nervous: dizziness, insomnia; leg cramps; nervousness; paresthesia

Respiratory: dyspnea

Skin: hyper-pigmentation; acanthosis nigricans; maculopapular rash; urticaria; dry skin; sweating

Other: migraine

Hypersensitivity reactions: An apparent hypersensitivity reaction has been reported rarely that has included one or more of the following features: anaphylaxis, angioedema, urticaria, flushing, dyspnea, tongue edema, larynx edema, face edema, peripheral edema, laryngismus, and vesiculobullous rash.

Clinical Laboratory Abnormalities

Chemistry: Elevations in serum transaminases (see **WARNINGS**, ***Liver Dysfunction***), LDH, fasting glucose, uric acid, total bilirubin, and amylase; reductions in phosphorus

Table 13 Treatment-Emergent Adverse Events by Dose Level in ≥5% of Patients; Events Considered At Least Remotely Related to Study Medication

	Placebo-Controlled Studies NIASPAN Treatment†						
			Recommended Daily Maintenance Doses			Greater Than Recommended Daily Doses	
	Placebo (n=157) %	500mg‡ (n=87) %	1000mg (n=110) %	1500mg (n=136) %	2000mg (n=95) %	2500mg‡ (n=49) %	3000mg‡ (n=46) %
Headache	15	5*	9	11	8	4*	4
Pain	3	1	2	5	3	0	2
Pain, Abdominal	3	3	2	3	5	0	0
Diarrhea	8	6	7	6	8	10	11
Dyspepsia	8	2	4	5	5	6	0
Nausea	4	2	5	3	8	10	4
Vomiting	2	0	2	3	8*	8	2
Rhinitis	7	2	5	4	3	0	0
Pruritus	1	6	<1	3	1	0	0
Rash	<1	5	5	4	0	0	0

Note: Percentages are calculated from the total number of patients in each column. AEs are reported at the lowest dose where they occurred.
†Pooled results from placebo-controlled studies; for NIASPAN, n=245 and mean treatment duration = 17 weeks. Number of NIASPAN patients (n) are not additive across doses.
‡The 500mg, 2500mg and 3000mg/day doses are outside the recommended daily maintenance dosing range; see **DOSAGE AND ADMINISTRATION**.
* Significantly different from placebo at $p \leq 0.05$; Chi-square test (cell size>5), Fisher's Exact test (cell sizes≤5).
In general, the incidence of adverse events was higher in women compared to men.

Table 14. Recommended Dosing

	Week(s)	Daily Dose	NIASPAN Dosage
TITRATION SCHEDULE	1 to 4	500mg	1 NIASPAN 500mg tablet at bedtime
	5 to 8	1000mg	2 NIASPAN 500mg tablets at bedtime
	*	1500mg	2 NIASPAN 750mg tablets or 3 NIASPAN 500mg tablets at bedtime
	*	2000mg	2 NIASPAN 1000mg tablets or 4 NIASPAN 500mg tablets at bedtime

*After Week 8, titrate to patient response and tolerance. If response to 1000mg daily is inadequate, increase dose to 1500mg daily, may subsequently increase dose to 2000mg daily. Daily dose should not be increased more than 500mg in a 4-week period, and doses above 2000mg daily are not recommended. Women may respond at lower doses than men.

Hematology: Slight reductions in platelet counts and prolongation in prothrombin time (see **WARNINGS**)

DRUG ABUSE AND DEPENDENCE

Niacin is a non-narcotic drug. It has no known addiction potential in humans.

OVERDOSE

Supportive measures should be undertaken in the event of an overdosage.

DOSAGE AND ADMINISTRATION

NIASPAN should be taken at bedtime, after a low-fat snack, and doses should be individualized according to patient response. Therapy with NIASPAN must be initiated at 500mg qhs in order to reduce the incidence and severity of side effects which may occur during early therapy. The recommended dose escalation is shown in Table 14 below.
[See table 14 above]
Maintenance Dose:
The daily dosage of NIASPAN should not be increased by more than 500mg in any 4-week period. The recommended maintenance dose is 1000mg (two 500mg tablets) to 2000mg (two 1000mg tablets or four 500mg tablets) once daily at bedtime. Doses greater than 2000mg daily are not recommended. Women may respond at lower NIASPAN doses than men (see **CLINICAL PHARMACOLOGY**, *Gender Effect*).
If lipid response to NIASPAN alone is insufficient (see NCEP treatment guidelines; Table 11), or if higher doses of NIASPAN are not well tolerated, some patients may benefit from combination therapy with a bile acid binding resin or an HMG-CoA reductase inhibitor (See **WARNINGS**, **PRECAUTIONS, Drug Interactions, Concomitant Therapy** below, and **CLINICAL PHARMACOLOGY, NIASPAN Clinical Studies**)
Flushing of the skin (see **ADVERSE REACTIONS**) may be reduced in frequency or severity by pretreatment with aspirin (taken 30 minutes prior to NIASPAN dose) or non-steroidal anti-inflammatory drugs. Tolerance to this flushing develops rapidly over the course of several weeks. Flushing, pruritus, and gastrointestinal distress are also greatly reduced by slowly increasing the dose of niacin and avoiding administration on an empty stomach.

Equivalent doses of NIASPAN should **not** be substituted for sustained-release (modified-release, timed-release) niacin preparations or immediate-release (crystalline) niacin (see **WARNINGS**). Patients previously receiving other niacin products should be started with the recommended NIASPAN titration schedule (see Table 14), and the dose should subsequently be individualized based on patient response. Single-dose bioavailability studies have demonstrated that NIASPAN tablet strengths are not interchangeable.
If NIASPAN therapy is discontinued for an extended period, reinstitution of therapy should include a titration phase (see Table 14).
NIASPAN tablets should be taken whole and should not be broken, crushed or chewed before swallowing.
Concomitant Therapy
Concomitant Therapy with Lovastatin
Patients already receiving a stable dose of lovastatin who require TG-lowering or HDL-raising (e.g., to achieve NCEP non-HDL-C goals), may receive concomitant dosage titration with NIASPAN per NIASPAN recommended initial titration schedule (see Table 14, **DOSAGE AND ADMINISTRATION** section). For patients already receiving a stable dose of NIASPAN who require further LDL-lowering (e.g., to achieve NCEP LDL-C goals; Table 11), the usual recommended starting dose of lovastatin is 20mg once a day. Dose adjustments should be made at intervals of 4 weeks or more. Combination therapy with NIASPAN and lovastatin should not exceed doses of 2000mg and 40mg daily, respectively.
Dosage in Patients with Renal or Hepatic Insufficiency
Use of NIASPAN in patients with renal or hepatic insufficiency has not be studied. NIASPAN is contraindicated in patients with significant or unexplained hepatic dysfunction. NIASPAN should be used with caution in patients with renal insufficiency (see **WARNINGS, PRECAUTIONS**).

HOW SUPPLIED

NIASPAN is supplied as unscored, off-white capsule-shaped tablets containing 500, 750 or 1000mg of niacin in an extended-release formulation. Tablets are debossed KOS on one side and the tablet strength (500, 750 or 1000) on the other side. Tablets are supplied in bottles of 100 as shown below.

500mg tablets: bottles of 100 - NDC# 60598-001-01
750mg tablets: bottles of 100 - NDC# 60598-002-01
1000mg tablets: bottles of 100 - NDC# 60598-003-01
Store at room temperature (20 to 25°C or 68 to 77°F).

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Manufactured by:
Kos Pharmaceuticals, Inc.
Cranbury, NJ 08512

U.S. Patent Nos. 6,080,428; 6,129,930; 6,406,715 B1, 6,676,967; 6,746,691; 6,818,229; and other patents pending.
Shown in Product Identification Guide, page 319

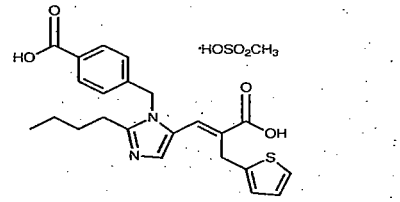
TEVETEN® ℞
[tē vē tĕn]
(eprosartan mesylate)
400 mg
600 mg

PRESCRIBING INFORMATION

USE IN PREGNANCY
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, TEVETEN® should be discontinued as soon as possible. See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

TEVETEN® (eprosartan mesylate) is a non-biphenyl non-tetrazole angiotensin II receptor (AT_1) antagonist. A selective non-peptide molecule, TEVETEN® is chemically described as the monomethanesulfonate of (*E*)-2-butyl-1-(*p*-carboxybenzyl)-α-2-thienylmethylimidazole-5-acrylic acid.
Its empirical formula is $C_{23}H_{24}N_2O_4S \cdot CH_4O_3S$ and molecular weight is 520.625. Its structural formula is:



Eprosartan mesylate is a white to off-white free-flowing crystalline powder that is insoluble in water, freely soluble in ethanol, and melts between 248°C and 250°C.
TEVETEN® is available as aqueous film-coated tablets containing eprosartan mesylate equivalent to 400 mg or 600 mg eprosartan zwitterion (pink, oval, non-scored tablets or white, non-scored, capsule-shaped tablets, respectively).

Inactive Ingredients

The 400 mg tablet contains the following: croscarmellose sodium, hypromellose, iron oxide red, iron oxide yellow, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, pregelatinized starch, and titanium dioxide. The 600 mg tablet contains crospovidone, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, pregelatinized starch, and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Angiotensin II (formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme [kininase II]), a potent vasoconstrictor, is the principal pressor agent of the renin-angiotensin system. Angiotensin II also stimulates aldosterone synthesis and secretion by the adrenal cortex, cardiac contraction, renal resorption of sodium, activity of the sympathetic nervous system, and smooth muscle cell growth. Eprosartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor found in many tissues (e.g., vascular smooth muscle, adrenal gland). There is also an AT_2 receptor found in many tissues but it is

Continued on next page

Vasotec I.V.—Cont.

VASOTEC I.V. was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril showed no drug-related changes in the following genotoxicity studies: rec-assay, reverse mutation assay with *E. coli,* sister chromatid exchange with cultured mammalian cells, the micronucleus test with mice, and in an *in vivo* cytogenic study using mouse bone marrow. There were no adverse effects on reproductive performance of male and female rats treated with up to 90 mg/kg/day of enalapril (26 times the MRHDD when compared on a body surface area basis).

Pregnancy

Pregnancy Categories C (first trimester) and *D* (second and third trimesters). See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*

Nursing Mothers

Enalapril and enalaprilat have been detected in human breast milk. Because of the potential for serious adverse reactions in nursing infants from enalapril, a decision should be made whether to discontinue nursing or to discontinue VASOTEC I.V., taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of VASOTEC I.V. did not include sufficient numbers of subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Evaluation of the hypertensive patient should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

ADVERSE REACTIONS

VASOTEC I.V. has been found to be generally well tolerated in controlled clinical trials involving 349 patients (168 with hypertension, 153 with congestive heart failure and 28 with coronary artery disease). The most frequent clinically significant adverse experience was hypotension (3.4 percent), occurring in eight patients (5.2 percent) with congestive heart failure, three (1.8 percent) with hypertension and one with coronary artery disease. Other adverse experiences occurring in greater than one percent of patients were: headache (2.9 percent) and nausea (1.1 percent).

Adverse experiences occurring in 0.5 to 1.0 percent of patients in controlled clinical trials included: myocardial infarction, fatigue, dizziness, fever, rash and constipation.

Angioedema: Angioedema has been reported in patients receiving enalaprilat, with an incidence higher in black than in non-black patients. Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with enalaprilat should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Cough: See PRECAUTIONS, *Cough.*

Enalapril Maleate

Since enalapril is converted to enalaprilat, those adverse experiences associated with enalapril might also be expected to occur with VASOTEC I.V.

The following adverse experiences have been reported with enalapril and, within each category, are listed in order of decreasing severity.

Body As A Whole: Syncope, orthostatic effects, anaphylactoid reactions (see WARNINGS, *Anaphylactoid reactions during membrane exposure*), chest pain, abdominal pain, asthenia.

Cardiovascular: Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, *Hypotension*); pulmonary embolism and infarction; pulmonary edema; rhythm disturbances including atrial tachycardia and bradycardia; atrial fibrillation; orthostatic hypotension; angina pectoris; palpitation, Raynaud's phenomenon.

Digestive: Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular [proven on rechallenge] or cholestatic jaundice) (see WARNINGS, *Hepatic Failure*), melena, diarrhea, vomiting, dyspepsia, anorexia, glossitis, stomatitis, dry mouth.

Hematologic: Rare cases of neutropenia, thrombocytopenia and bone marrow depression.

Musculoskeletal: Muscle cramps.

Nervous/Psychiatric: Depression, vertigo, confusion, ataxia, somnolence, insomnia, nervousness, peripheral neuropathy (e.g. paresthesia, dysesthesia), dream abnormality.

Respiratory: Bronchospasm, dyspnea, pneumonia, bronchitis, cough, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection, pulmonary infiltrates, eosinophilic pneumonitis.

Skin: Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, pemphigus, herpes zoster, erythema multiforme, urticaria, pruritus, alopecia, flushing, diaphoresis, photosensitivity.

Special Senses: Blurred vision, taste alteration, anosmia, tinnitus, conjunctivitis, dry eyes, tearing.

Urogenital: Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), urinary tract infection, flank pain, gynecomastia, impotence.

Miscellaneous: A symptom complex has been reported which may include some or all of the following: a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia/myositis, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash and other dermatologic manifestations.

Hypotension: Combining the results of clinical trials in patients with hypertension or congestive heart failure, hypotension (including postural hypotension, and other orthostatic effects) was reported in 2.3 percent of patients following the initial dose of enalapril or during extended therapy. In the hypertensive patients, hypotension occurred in 0.9 percent and syncope occurred in 0.5 percent of patients. Hypotension or syncope was a cause for discontinuation of therapy in 0.1 percent of hypertensive patients. (See WARNINGS.)

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*

Clinical Laboratory Test Findings

Serum Electrolytes: Hyperkalemia (see PRECAUTIONS), hyponatremia.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2 percent of patients with essential hypertension treated with enalapril alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.)

Hematology: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g percent and 1.0 vol percent, respectively) occur frequently in hypertensive patients treated with enalapril but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1 percent of patients discontinued therapy due to anemia. Hemolytic anemia, including cases of hemolysis in patients with G-6-PD deficiency, has been reported; a causal relationship to enalapril cannot be excluded.

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin have occurred (see WARNINGS, *Hepatic Failure*).

OVERDOSAGE

In clinical studies, some hypertensive patients received a maximum dose of 80 mg of enalaprilat intravenously over a fifteen minute period. At this high dose, no adverse effects beyond those as associated with the recommended dosages were observed.

A single intravenous dose of ≤ 4167 mg/kg of enalaprilat was associated with lethality in female mice. No lethality occurred after an intravenous dose of 3472 mg/kg.

The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution.

Enalaprilat may be removed from general circulation by hemodialysis and has been removed from neonatal circulation by peritoneal dialysis. (See WARNINGS, *Anaphylactoid reactions during membrane exposure.*)

DOSAGE AND ADMINISTRATION

FOR INTRAVENOUS ADMINISTRATION ONLY

The dose in hypertension is 1.25 mg every six hours administered intravenously over a five minute period. A clinical response is usually seen within 15 minutes. Peak effects after the first dose may not occur for up to four hours after dosing. The peak effects of the second and subsequent doses may exceed those of the first.

No dosage regimen for VASOTEC I.V. has been clearly demonstrated to be more effective in treating hypertension than 1.25 mg every six hours. However, in controlled clinical studies in hypertension, doses as high as 5 mg every six hours were well tolerated for up to 36 hours. There has been inadequate experience with doses greater than 20 mg per day.

In studies of patients with hypertension, VASOTEC I.V. has not been administered for periods longer than 48 hours. In other studies, patients have received VASOTEC I.V. for as long as seven days.

The dose for patients being converted to VASOTEC I.V. from oral therapy for hypertension with enalapril maleate is 1.25 mg every six hours. For conversion from intravenous to oral therapy, the recommended initial dose of Tablets VASOTEC (Enalapril Maleate) is 5 mg once a day with subsequent dosage adjustments as necessary.

Patients on Diuretic Therapy

For patients on diuretic therapy the recommended starting dose for hypertension is 0.625 mg administered intravenously over a five minute period. A clinical response is usually seen within 15 minutes. Peak effects after the first dose may not occur for up to four hours after dosing, although most of the effect is usually apparent within the first hour. If after one hour there is an inadequate clinical response, the 0.625 mg dose may be repeated. Additional doses of 1.25 mg may be administered at six hour intervals.

For conversion from intravenous to oral therapy, the recommended initial dose of Tablets VASOTEC (Enalapril Maleate) for patients who have responded to 0.625 mg of enalaprilat every six hours is 2.5 mg once a day with subsequent dosage adjustment as necessary.

Dosage Adjustment in Renal Impairment

The usual dose of 1.25 mg of enalaprilat every six hours is recommended for patients with a creatinine clearance >30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≤30 mL/min (serum creatinine ≥3 mg/dL), the initial dose is 0.625 mg. (See WARNINGS.)

If after one hour there is an inadequate clinical response, the 0.625 mg dose may be repeated. Additional doses of 1.25 mg may be administered at six hour intervals.

For dialysis patients, see below, *Patients at Risk of Excessive Hypotension.*

For conversion from intravenous to oral therapy, the recommended initial dose of Tablets VASOTEC (Enalapril Maleate) is 5 mg once a day for patients with creatinine clearance >30 mL/min and 2.5 mg once daily for patients with creatinine clearance ≤30 mL/min. Dosage should then be adjusted according to blood pressure response.

Patients at Risk of Excessive Hypotension

Hypertensive patients at risk of excessive hypotension include those with the following concurrent conditions or characteristics: heart failure, hyponatremia, high dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology (see WARNINGS). Single doses of enalaprilat as low as 0.2 mg have produced excessive hypotension in normotensive patients with these diagnoses. Because of the potential for an extreme hypotensive response in these patients, therapy should be started under very close medical supervision. The starting dose should be no greater than 0.625 mg administered intravenously over a period of no less than five minutes and preferably longer (up to one hour).

Patients should be followed closely whenever the dose of enalaprilat is adjusted and/or diuretic is increased.

Administration

VASOTEC I.V. should be administered as a slow intravenous infusion, as indicated above, over at least five minutes. It may be administered as provided or diluted with up to 50 mL of a compatible diluent.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to use whenever solution and container permit.

Compatibility and Stability

VASOTEC I.V. as supplied and mixed with the following intravenous diluents has been found to maintain full activity for 24 hours at room temperature:

5 percent Dextrose Injection

0.9 percent Sodium Chloride Injection

0.9 percent Sodium Chloride Injection in 5 percent Dextrose

5 percent Dextrose in Lactated Ringer's Injection

McGaw ISOLYTE** E.

**Registered trademark of American Hospital Supply Corporation.

HOW SUPPLIED

No. 3824—VASOTEC I.V., 1.25 mg per mL, is a clear, colorless solution and is supplied in vials containing 1 mL and 2 mL.

NDC 0006-3824-01, 1 mL vials

NDC 0006-3824-04, 2 mL vials.

Storage

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature].

7875733 Issued January 2002

ZOCOR® Tablets

℞

[zō'kōr]

(simvastatin)

DESCRIPTION

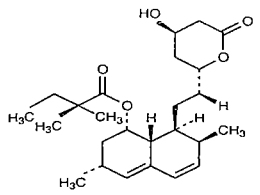
ZOCOR[1] (simvastatin) is a lipid-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus.* After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.

Simvastatin is butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1*S*-[1α,3α,7β,8β(2*S**,4*S**),-8aβ]]. The empirical formula of simvastatin is $C_{25}H_{38}O_5$ and its molecular weight is 418.57. Its structural formula is:

[See chemical structure at top of next column]

Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol and ethanol.

Tablets ZOCOR for oral administration contain either 5 mg, 10 mg, 20 mg, 40 mg or 80 mg of simvastatin and the fol-



lowing inactive ingredients: cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, lactose, magnesium stearate, starch, talc, titanium dioxide and other ingredients. Butylated hydroxyanisole is added as a preservative.

[1]Registered trademark of MERCK & CO., Inc.

CLINICAL PHARMACOLOGY

The involvement of low-density lipoprotein cholesterol (LDL-C) in atherogenesis has been well-documented in clinical and pathological studies, as well as in many animal experiments. Epidemiological studies have established that elevated plasma levels of total cholesterol (total-C), LDL-C, and apolipoprotein B (Apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of high-density lipoprotein cholesterol (HDL-C) and its transport complex, Apo A-I, are associated with decreased cardiovascular risk. High plasma triglycerides (TG) and cholesterol-enriched TG-rich lipoproteins, including very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis. Elevated plasma TG are frequently found in a triad with low HDL-C and small LDL particles, as well as in association with non-lipid metabolic risk factors for CHD. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL-C or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined. In the Scandinavian Simvastatin Survival Study (4S), the effect of improving lipoprotein levels with ZOCOR on total mortality was assessed in 4,444 patients with CHD and baseline total cholesterol (total-C) 212-309 mg/dL (5.5-8.0 mmol/L). The patients were followed for a median of 5.4 years. In this multicenter, randomized, double-blind, placebo-controlled study, ZOCOR significantly reduced the risk of mortality by 30% (11.5% vs 8.2%, placebo vs ZOCOR); of CHD mortality by 42% (8.5% vs 5.0%); and of having a hospital-verified non-fatal myocardial infarction by 37% (19.6% vs 12.9%). Furthermore, ZOCOR significantly reduced the risk for undergoing myocardial revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 37% (17.2% vs 11.4%) [see CLINICAL PHARMACOLOGY, *Clinical Studies*].

ZOCOR has been shown to reduce both normal and elevated LDL-C concentrations. LDL is formed from very-low-density lipoprotein (VLDL) and is catabolized predominantly by the high-affinity LDL receptor. The mechanism of the LDL-lowering effect of ZOCOR may involve both reduction of VLDL cholesterol concentration, and induction of the LDL receptor, leading to reduced production and/or increased catabolism of LDL-C. Apo B also falls substantially during treatment with ZOCOR. As each LDL particle contains one molecule of Apo B, and since in patients with predominant elevations in LDL-C (without accompanying elevation in VLDL) little Apo B is found in other lipoproteins, this strongly suggests that ZOCOR does not merely cause cholesterol to be lost from LDL, but also reduces the concentration of circulating LDL particles. In addition, ZOCOR reduces VLDL and TG and increases HDL-C. The effects of ZOCOR on Lp(a), fibrinogen, and certain other independent biochemical risk markers for CHD are unknown.

ZOCOR is a specific inhibitor of HMG-CoA reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate. The conversion of HMG-CoA to mevalonate is an early step in the biosynthetic pathway for cholesterol.

Pharmacokinetics

Simvastatin is a lactone that is readily hydrolyzed *in vivo* to the corresponding β-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Inhibition of HMG-CoA reductase is the basis for an assay in pharmacokinetic studies of the β-hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors) in plasma following administration of simvastatin.

Following an oral dose of ^{14}C-labeled simvastatin in man, 13% of the dose was excreted in urine and 60% in feces. The latter represents absorbed drug equivalents excreted in bile, as well as any unabsorbed drug. Plasma concentrations of total radioactivity (simvastatin plus ^{14}C-metabolites) peaked at 4 hours and declined rapidly to about 10% of peak by 12 hours postdose. Absorption of simvastatin, estimated relative to an intravenous reference dose, in each of two animal species tested, averaged about 85% of an oral dose. In animal studies, after oral dosing, simvastatin achieved substantially higher concentrations in the liver than in nontarget tissues. Simvastatin undergoes extensive first-pass extraction in the liver, its primary site of action, with subsequent excretion of drug equivalents in the bile. As a consequence of extensive hepatic extraction of simvastatin (estimated to be > 60% in man), the availability of drug to the general circulation is low. In a single-dose study in nine healthy subjects, it was estimated that less than 5% of an oral dose of simvastatin reaches the general circulation as active inhibitors. Following administration of simvastatin tablets, the coefficient of variation, based on between-subject variability, was approximately 48% for the area under the concentration-time curve (AUC) for total inhibitory activity in the general circulation.

Both simvastatin and its β-hydroxyacid metabolite are highly bound (approximately 95%) to human plasma proteins. Animal studies have not been performed to determine whether simvastatin crosses the blood-brain and placental barriers. However, when radiolabeled simvastatin was administered to rats, simvastatin-derived radioactivity crossed the blood-brain barrier.

The major active metabolites of simvastatin present in human plasma are the β-hydroxyacid of simvastatin and its 6'-hydroxy, 6'-hydroxymethyl, and 6'-exomethylene derivatives. Peak plasma concentrations of both active and total inhibitors were attained within 1.3 to 2.4 hours postdose. While the recommended therapeutic dose range is 5 to 80 mg/day, there was no substantial deviation from linearity of AUC of inhibitors in the general circulation with an increase in dose to as high as 120 mg. Relative to the fasting state, the plasma profile of inhibitors was not affected when simvastatin was administered immediately before an American Heart Association recommended low-fat meal.

In a study including 16 elderly patients between 70 and 78 years of age who received ZOCOR 40 mg/day, the mean plasma level of HMG-CoA reductase inhibitory activity was increased approximately 45% compared with 18 patients between 18-30 years of age. Clinical study experience in the elderly (n=1522), suggests that there were no overall differences in safety between elderly and younger patients (see PRECAUTIONS, *Geriatric Use*).

Kinetic studies with another reductase inhibitor, having a similar principal route of elimination, have suggested that for a given dose level higher systemic exposure may be achieved in patients with severe renal insufficiency (as measured by creatinine clearance).

In a study of 12 healthy volunteers, simvastatin at the 80-mg dose had no effect on the metabolism of the probe cytochrome P450 isoform 3A4 (CYP3A4) substrates midazolam and erythromycin. This indicates that simvastatin is not an inhibitor of CYP3A4, and, therefore, is not expected to affect the plasma levels of other drugs metabolized by CYP3A4.

The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Potent inhibitors of CYP3A4 can raise the plasma levels of HMG-CoA reductase inhibitory activity and increase the risk of myopathy (see WARNINGS, *Myopathy/Rhabdomyolysis* and PRECAUTIONS, *Drug Interactions*).

Simvastatin is a substrate for CYP3A4 (see PRECAUTIONS, *Drug Interactions*). Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma concentrations of drugs metabolized by CYP3A4. In one study[2], 10 subjects consumed 200 mL of double-strength grapefruit juice (one can of frozen concentrate diluted with one rather than 3 cans of water) three times daily for 2 days and an additional 200 mL double-strength grapefruit juice together with, and 30 and 90 minutes following, a single dose of 60 mg simvastatin on the third day. This regimen of grapefruit juice resulted in mean increases in the concentration (as measured by the area under the concentration-time curve) of active and total HMG-CoA reductase inhibitory activity [measured using a radioenzyme inhibition assay both before (for active inhibitors) and after (for total inhibitors) base hydrolysis] of 2.4-fold and 3.6-fold, respectively, and of simvastatin and its β-hydroxyacid metabolite [measured using a chemical assay — liquid chromatography/tandem mass spectrometry] of 16-fold and 7-fold, respectively. In a second study, 16 subjects consumed one 8 oz glass of single-strength grapefruit juice (one can of frozen concentrate diluted with 3 cans of water) with breakfast for 3 consecutive days and a single dose of 20 mg simvastatin in the evening of the third day. This regimen of grapefruit juice resulted in a mean increase in the plasma concentration (as measured by the area under the concentration-time curve) of active and total HMG-CoA reductase inhibitory activity [using a validated enzyme inhibition assay different from that used in the first[2] study, both before (for active inhibitors) and after (for total inhibitors) base hydrolysis] of 1.13-fold and 1.18-fold, respectively, and of simvastatin and its β-hydroxyacid metabolite [measured using a chemical assay — liquid chromatography/tandem mass spectrometry] of 1.88-fold and 1.31-fold, respectively. The effect of amounts of grapefruit juice between those used in these two studies on simvastatin pharmacokinetics has not been studied.

TABLE 1
Summary of Heart Protection Study Results

Endpoint	ZOCOR (N=10,269) n (%)[†]	Placebo (N=10,267) n (%)[†]	Risk Reduction (%) (95% CI)	p-Value
Primary				
Mortality	1,328 (12.9)	1,507 (14.7)	13 (6-19)	p=0.0003
CHD mortality	587 (5.7)	707 (6.9)	18 (8-26)	p=0.0005
Secondary				
Non-fatal MI	357 (3.5)	574 (5.6)	38 (30-46)	p<0.0001
Stroke	444 (4.3)	585 (5.7)	25 (15-34)	p<0.0001
Tertiary				
Coronary revascularization	513 (5)	725 (7.1)	30 (22-38)	p<0.0001
Peripheral and other non-coronary revascularization	450 (4.4)	532 (5.2)	16 (5-26)	p=0.006

[†] n = number of patients with indicated event

[2] Lilja JJ, Kivisto KT, Neuvonen PJ. Clin Pharmacol Ther 1998;64(5):477-83.

Clinical Studies in Adults

Reductions in Risk of CHD Mortality and Cardiovascular Events

In 4S, the effect of therapy with ZOCOR on total mortality was assessed in 4,444 patients with CHD and baseline total cholesterol 212-309 mg/dL (5.5-8.0 mmol/L). In this multicenter, randomized, double-blind, placebo-controlled study, patients were treated with standard care, including diet, and either ZOCOR 20-40 mg/day (n=2,221) or placebo (n=2,223) for a median duration of 5.4 years. After six weeks of treatment with ZOCOR the median (25th and 75th percentile) changes in LDL-C, TG, and HDL-C were -39% (-46, -31%), -19% (-31, 0%), and 6% (-3, 17%). Over the course of the study, treatment with ZOCOR led to mean reductions in total-C, LDL-C and TG of 25%, 35%, and 10%, respectively, and a mean increase in HDL-C of 8%. ZOCOR significantly reduced the risk of mortality by 30%, (p=0.0003, 182 deaths in the ZOCOR group vs 256 deaths in the placebo group). The risk of CHD mortality was significantly reduced by 42% (p=0.00001, 111 vs 189 deaths). There was no statistically significant difference between groups in non-cardiovascular mortality. ZOCOR also significantly decreased the risk of having major coronary events (CHD mortality plus hospital-verified and silent non-fatal myocardial infarction [MI]) by 34% (p<0.00001, 431 vs 622 patients with one or more events). The risk of having a hospital-verified non-fatal MI was reduced by 37%. ZOCOR significantly reduced the risk for undergoing myocardial revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 37%, (p<0.00001, 252 vs 383 patients). Furthermore, ZOCOR significantly reduced the risk of fatal plus non-fatal cerebrovascular events (combined stroke and transient ischemic attacks) by 28% (p=0.033, 75 vs 102 patients). ZOCOR reduced the risk of major coronary events to a similar extent across the range of baseline total and LDL cholesterol levels. Because there were only 53 female deaths, the effect of ZOCOR on mortality in women could not be adequately assessed. However, ZOCOR significantly lessened the risk of having major coronary events by 34% (60 vs 91 women with one or more event). The randomization was stratified by angina alone (21% of each treatment group) or a previous MI. Because there were only 57 deaths among the patients with angina alone at baseline, the effect of ZOCOR on mortality in this subgroup could not be adequately assessed. However, trends in reduced coronary mortality, major coronary events and revascularization procedures were consistent between this group and the total study cohort. Additionally, in this study, 1,021 of the patients were 65 and older. Cholesterol reduction with simvastatin resulted in similar decreases in relative risk for total mortality, CHD mortality, and major coronary events in these elderly patients, compared with younger patients.

The Heart Protection Study (HPS) was a large, multicenter, placebo-controlled, double-blind study with a mean duration of 5 years conducted in 20,536 patients (10,269 on

Continued on next page

Zocor—Cont.

ZOCOR 40 mg and 10,267 on placebo). Patients were allocated to treatment using a covariate adaptive method[3] which took into account the distribution of 10 important baseline characteristics of patients already enrolled and minimized the imbalance of those characteristics across the groups. Patients had a mean age of 64 years (range 40-80 years), were 97% Caucasian and were at high risk of developing a major coronary event because of existing coronary heart disease (65%), diabetes (Type 2, 26%; Type 1, 3%), history of stroke or other cerebrovascular disease (16%), peripheral vessel disease (33%), or hypertension in males 65 years of age and older (6%). At baseline, 3,421 patients (17%) had LDL-C levels below 100 mg/dL, of whom 953 (5%) had LDL-C levels below 80 mg/dL; 7,068 patients (34%) had levels between 100 and 130 mg/dL; and 10,047 patients (49%) had levels greater than 130 mg/dL.

[3] D.R. Taves, Minimization: a new method of assigning patients to treatment and control groups. Clin. Pharmacol. Ther. **15** (1974), pp. 443-453

The HPS results showed that ZOCOR 40 mg/day significantly reduced: total and CHD mortality; non-fatal myocardial infarctions, stroke, and revascularization procedures (coronary and non-coronary) (see Table 1).

[See table 1 at top of previous page]

Two composite endpoints were defined in order to have sufficient events to assess relative risk reductions across a range of baseline characteristics (see Figure 1). A composite of major coronary events (MCE) was comprised of CHD mortality and non-fatal MI (analyzed by time-to-first event; 898 patients treated with ZOCOR had events and 1,212 patients on placebo had events). A composite of major vascular events (MVE) was comprised of MCE, stroke and revascularization procedures including coronary, peripheral and other non-coronary procedures (analyzed by time-to-first event; 2,033 patients treated with ZOCOR had events and 2,585 patients on placebo had events). Significant relative risk reductions were observed for both composite endpoints (27% for MCE and 24% for MVE, $p<0.0001$). Furthermore, treatment with ZOCOR produced significant relative risk reductions for all components of the composite endpoints. The risk reductions produced by ZOCOR in both MCE and MVE were evident and consistent regardless of cardiovascular disease related medical history at study entry (i.e., CHD alone; or peripheral vascular disease, cerebrovascular disease, diabetes or treated hypertension, with or without CHD), gender, age, creatinine levels up to the entry limit of 2.3 mg/dL, baseline levels of LDL-C, HDL-C, apolipoprotein B and A-1, baseline concomitant cardiovascular medications (i.e., aspirin, beta blockers, or calcium channel blockers), smoking status, alcohol intake, or obesity. Diabetics showed risk reductions for MCE and MVE due to ZOCOR treatment regardless of baseline HbA1c levels or obesity with the greatest effects seen for diabetics without CHD.

[See figure 1 above]

Angiographic Studies

In the Multicenter Anti-Atheroma Study, the effect of simvastatin on atherosclerosis was assessed by quantitative coronary angiography in hypercholesterolemic patients with coronary heart disease. In this randomized, double-blind, controlled study, patients were treated with simvastatin 20 mg/day or placebo. Angiograms were evaluated at baseline, two and four years. The co-primary study endpoints were mean change per-patient in minimum and mean lumen diameters, indicating focal and diffuse disease, respectively. Simvastatin significantly slowed the progression of lesions as measured in the Year 4 angiogram by both parameters, as well as by change in percent diameter stenosis. In addition, simvastatin significantly decreased the proportion of patients with new lesions and with new total occlusions.

Modifications of Lipid Profiles

Primary Hypercholesterolemia (Fredrickson type IIa and IIb)

ZOCOR has been shown to be highly effective in reducing total-C and LDL-C in heterozygous familial and non-familial forms of hypercholesterolemia and in mixed hyperlipidemia. A marked response was seen within 2 weeks, and the maximum therapeutic response occurred within 4-6 weeks. The response was maintained during chronic therapy. Furthermore, improving lipoprotein levels with ZOCOR improved survival in patients with CHD and hypercholesterolemia treated with 20-40 mg/day for a median of 5.4 years.

In a multicenter, double-blind, placebo-controlled, dose-response study in patients with familial or non-familial hypercholesterolemia, ZOCOR given as a single dose in the evening (the recommended dosing) was similarly effective as when given on a twice-daily basis. ZOCOR consistently and significantly decreased total-C, LDL-C, total-C/HDL-C ratio, and LDL-C/HDL-C ratio. ZOCOR also decreased TG and increased HDL-C.

The results of studies depicting the mean response to simvastatin in patients with primary hypercholesterolemia and combined (mixed) hyperlipidemia are presented in Table 2.

[See table 2 above]

In the Upper Dose Comparative Study, the mean reduction in LDL-C was 47% at the 80-mg dose. Of the 664 patients randomized to 80 mg, 475 patients with plasma TG ≤ 200 mg/dL had a median reduction in TG of 21%, while in 189 patients with TG > 200 mg/dL, the median reduction in TG was 36%. In these studies, patients with TG > 350 mg/dL were excluded.

In the Multi-Center Combined Hyperlipidemia Study, a randomized, 3-period crossover study, 130 patients with combined hyperlipidemia (LDL-C>130 mg/dL and TG: 300-700 mg/dL) were treated with placebo, ZOCOR 40, and 80 mg/day for 6 weeks. In a dose-dependent manner ZOCOR 40 and 80 mg/day, respectively, decreased mean LDL-C by 29 and 36% (placebo: +2%) and median TG levels by 28 and 33% (placebo: 4%), and increased mean HDL-C by 13 and 16% (placebo: 3%) and apolipoprotein A-I by 8 and 11% (placebo: 4%).

Hypertriglyceridemia (Fredrickson type IV)

The results of a subgroup analysis in 74 patients with type IV hyperlipidemia from a 130-patient, double-blind, placebo-controlled, 3-period crossover study are presented in Table 3. The median baseline values (mg/dL) for the patients in this study were: total-C = 254, LDL-C = 135, HDL-C = 36, TG = 404, VLDL-C = 83, and non-HDL-C = 215.

[See table 3 above]

Dysbetalipoproteinemia (Fredrickson type III)

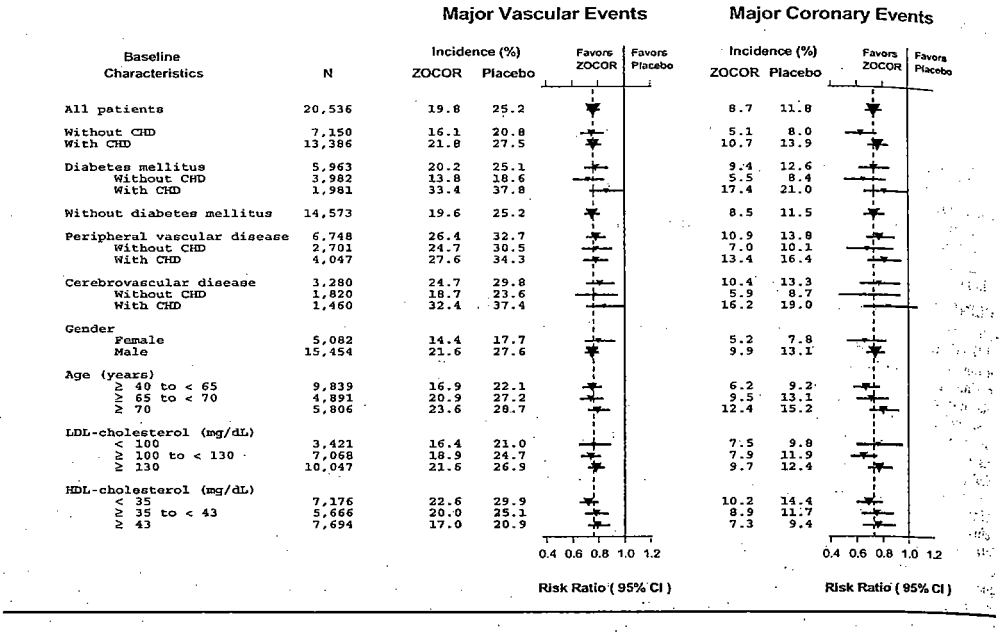
The results of a subgroup analysis in 7 patients with type III hyperlipidemia (dysbetalipoproteinemia) (apo E2/2) (VLDL-C/TG>0.25) from a 130-patient, double-blind, placebo-controlled, 3-period crossover study are presented in Table 4. In this study the median baseline values (mg/dL) were: total-C = 324, LDL-C = 121, HDL-C = 31, TG = 411, VLDL-C = 170, and non-HDL-C = 291.

[See table 4 at top of next page]

Homozygous Familial Hypercholesterolemia

In a controlled clinical study, 12 patients 15-39 years of age with homozygous familial hypercholesterolemia received simvastatin 40 mg/day in a single dose or in 3 divided doses, or 80 mg/day in 3 divided doses. Eleven of the 12 patients had reductions in LDL-C. In those patients with reductions, the mean LDL-C changes for the 40- and 80-mg doses were 14% (range 8% to 23%, median 12%) and 30% (range 14% to 46%, median 29%), respectively. One patient had an increase of 15% in LDL-C. Another patient with absent LDL-C receptor function had an LDL-C reduction of 41% with the 80-mg dose.

Figure 1
The Effects of Treatment with ZOCOR on Major Vascular Events and Major Coronary Events in HPS



N= number of patients in each subgroup. The inverted triangles are point estimates of the relative risk, with their 95% confidence intervals represented as a line. The area of a triangle is proportional to the number of patients with MVE or MCE in the subgroup relative to the number with MVE or MCE, respectively, in the entire study population. The vertical solid line represents a relative risk of one. The vertical dashed line represents the point estimate of relative risk in the entire study population.

TABLE 2
Mean Response in Patients with Primary Hypercholesterolemia and Combined (mixed) Hyperlipidemia
(Mean Percent Change from Baseline After 6 to 24 Weeks)

TREATMENT	N	TOTAL-C	LDL-C	HDL-C	TG†
Lower Dose Comparative Study					
(Mean % Change at Week 6)					
ZOCOR 5 mg q.p.m.	109	-19	-26	10	-12
ZOCOR 10 mg q.p.m.	110	-23	-30	12	-15
Scandinavian Simvastatin Survival Study					
(Mean % Change at Week 6)					
Placebo	2223	-1	-1	0	-2
ZOCOR 20 mg q.p.m.	2221	-28	-38	8	-19
Upper Dose Comparative Study					
(Mean % Change Averaged at Weeks 18 and 24)					
ZOCOR 40 mg q.p.m.	433	-31	-41	9	-18
ZOCOR 80 mg q.p.m.	664	-36	-47	8	-24
Multi-Center Combined Hyperlipidemia Study					
(Mean % Change at Week 6)					
Placebo	125	1	2	3	-4
ZOCOR 40 mg q.p.m.	123	-25	-29	13	-28
ZOCOR 80 mg q.p.m.	124	-31	-36	16	-33

† median percent change

TABLE 3
Six-week, Lipid-lowering Effects of Simvastatin in Type IV Hyperlipidemia
Median Percent Change (25th and 75th percentile) from Baseline

TREATMENT	N	Total-C	LDL-C	HDL-C	TG	VLDL-C	Non-HDL-C
Placebo	74	+2 (-7, +7)	+1 (-8, +14)	+3 (-3, +10)	-9 (-25, +13)	-7 (-25, +11)	+1 (-9, +8)
ZOCOR 40 mg/day	74	-25 (-34, -19)	-28 (-40, -17)	+11 (+5, +23)	-29 (-43, -16)	-37 (-54,-23)	-32 (-42, -23)
ZOCOR 80 mg/day	74	-32 (-38, -24)	-37 (-46, -26)	+15 (+5, +23)	-34 (-45, -18)	-41 (-57, -28)	-38 (-49, -32)

Endocrine Function

In clinical studies, simvastatin did not impair adrenal reserve or significantly reduce basal plasma cortisol concentration. Small reductions from baseline in basal plasma testosterone in men were observed in clinical studies with simvastatin, an effect also observed with other inhibitors of HMG-CoA reductase and the bile acid sequestrant cholestyramine. There was no effect on plasma gonadotropin levels. In a placebo-controlled, 12-week study there was no significant effect of simvastatin 80 mg on the plasma testosterone response to human chorionic gonadotropin (hCG). In another 24-week study, simvastatin 20-40 mg had no detectable effect on spermatogenesis. In 4S, in which 4,444 patients were randomized to simvastatin 20-40 mg/day or placebo for a median duration of 5.4 years, the incidence of male sexual adverse events in the two treatment groups was not significantly different. Because of these factors, the small changes in plasma testosterone are unlikely to be clinically significant. The effects, if any, on the pituitary-gonadal axis in pre-menopausal women are unknown.

Clinical Studies in Adolescents

In a double-blind, placebo-controlled study, 175 patients (99 adolescent boys and 76 post-menarchal girls) 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolemia (heFH) were randomized to simvastatin (n=106) or placebo (n=67) for 24 weeks (base study). Inclusion in the study required a baseline LDL-C level between 160 and 400 mg/dL and at least one parent with an LDL-C level >189 mg/dL. The dosage of simvastatin (once daily in the evening) was 10 mg for the first 8 weeks, 20 mg for the second 8 weeks, and 40 mg thereafter. In a 24-week extension, 144 patients elected to continue therapy and received simvastatin 40 mg or placebo.

ZOCOR significantly decreased plasma levels of total-C, LDL-C, and Apo B (see Table 5). Results from the extension at 48 weeks were comparable to those observed in the base study.

[See table 5 at right]

After 24 weeks of treatment, the mean achieved LDL-C value was 124.9 mg/dL (range: 64.0-289.0 mg/dL) in the ZOCOR 40 mg group compared to 207.8 mg/dL (range: 128.0-334.0 mg/dL) in the placebo group.

The safety and efficacy of doses above 40 mg daily have not been studied in children with heterozygous familial hypercholesterolemia. The long-term efficacy of simvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

INDICATIONS AND USAGE

Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol (see National Cholesterol Education Program [NCEP] Treatment Guidelines, below).

In patients with CHD or at high risk of CHD, ZOCOR can be started simultaneously with diet.

Reductions in Risk of CHD Mortality and Cardiovascular Events

In patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, ZOCOR is indicated to:

- Reduce the risk of total mortality by reducing CHD deaths.
- Reduce the risk of non-fatal myocardial infarction and stroke.
- Reduce the need for coronary and non-coronary revascularization procedures.

Patients with Hypercholesterolemia Requiring Modifications of Lipid Profiles

ZOCOR is indicated to:

- Reduce elevated total-C, LDL-C, Apo B, and TG, and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson types IIa and IIb[4]).
- Treat patients with hypertriglyceridemia (Fredrickson type IV hyperlipidemia).
- Treat patients with primary dysbetalipoproteinemia (Fredrickson type III hyperlipidemia).
- Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

Adolescent Patients with Heterozygous Familial Hypercholesterolemia (HeFH)

ZOCOR is indicated as an adjunct to diet to reduce total-C, LDL-C, and Apo B levels in adolescent boys and girls who are at least one year post-menarche, 10-17 years of age, with heterozygous familial hypercholesterolemia, if after an adequate trial of diet therapy the following findings are present:

1. LDL cholesterol remains ≥190 mg/dL; or
2. LDL cholesterol remains ≥160 mg/dL and
   - There is a positive family history of premature cardiovascular disease (CVD) or
   - Two or more other CVD risk factors are present in the adolescent patient

The minimum goal of treatment in pediatric and adolescent patients is to achieve a mean LDL-C <130 mg/dL. The optimal age at which to initiate lipid-lowering therapy to decrease the risk of symptomatic adulthood CAD has not been determined.

TABLE 4
Six-week, Lipid-lowering Effects of Simvastatin in Type III Hyperlipidemia
Median Percent Change (min,max) from Baseline

TREATMENT	N	Total-C	LDL-C + IDL	HDL-C	TG	VLDL-C+IDL	Non-HDL-C
Placebo	7	-8 (-24, +34)	-8 (-27, +23)	-2 (-21, +16)	+4 (-22, +90)	-4 (-28, +78)	-8 (-26, -39)
ZOCOR 40 mg/day	7	-50 (-66, -39)	-50 (-60, -31)	+7 (-8, +23)	-41 (-74, -16)	-58 (-90, -37)	-57 (-72, -44)
ZOCOR 80 mg/day	7	-52 (-55, -41)	-51 (-57, -28)	+7 (-5, +29)	-38 (-58, +2)	-60 (-72, -39)	-59 (-61, -46)

TABLE 5
Lipid-lowering Effects of Simvastatin in Adolescent Patients with Heterozygous Familial Hypercholesterolemia
(Mean Percent Change from Baseline)

Dosage	Duration	N		Total-C	LDL-C	HDL-C	TG†	Apo B
Placebo	24 Weeks	67	% Change from Baseline (95% CI)	1.6 (-2.2, 5.3)	1.1 (-3.4, 5.5)	3.6 (-0.7, 8.0)	-3.2 (-11.8, 5.4)	-0.5 (-4.7, 3.6)
			Mean baseline, mg/dL (SD)	278.6 (51.8)	211.9 (49.0)	46.9 (11.9)	90.0 (50.7)	186.3 (38.1)
ZOCOR	24 Weeks	106	% Change from Baseline (95% CI)	-26.5 (-29.6, -23.3)	-36.8 (-40.5, -33.0)	8.3 (4.6, 11.9)	-7.9 (-15.8, 0.0)	-32.4 (-35.9, -29.0)
			Mean baseline, mg/dL (SD)	270.2 (44.0)	203.8 (41.5)	47.7 (9.0)	78.3 (46.0)	179.9 (33.8)

† median percent change

TABLE 6
NCEP Treatment Guidelines:
LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD† or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional)‡
2+ Risk factors (10-year risk ≤20%)	<130	≥130	10-year risk 10-20%: ≥130 10-year risk <10%: ≥160
0-1 Risk factor§	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

† CHD, coronary heart disease
‡ Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.
§ Almost all people with 0-1 risk factor have a 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

General Recommendations

Prior to initiating therapy with simvastatin, secondary causes for hypercholesterolemia (e.g., hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile performed to measure total-C, HDL-C, and TG. For patients with TG less than 400 mg/dL (< 4.5 mmol/L), LDL-C can be estimated using the following equation:

$$\text{LDL-C} = \text{total-C} - [(0.20 \times \text{TG}) + \text{HDL-C}]$$

For TG levels > 400 mg/dL (> 4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In many hypertriglyceridemic patients, LDL-C may be low or normal despite elevated total-C. In such cases, ZOCOR is not indicated.

Lipid determinations should be performed at intervals of no less than four weeks and dosage adjusted according to the patient's response to therapy.

The NCEP Treatment Guidelines are summarized in Table 6:

[See table 6 above]

After the LDL-C goal has been achieved, if the TG is still ≥200 mg/dL, non-HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

At the time of hospitalization for an acute coronary event, consideration can be given to initiating drug therapy at discharge if the LDL-C is ≥ 130 mg/dL (see NCEP Treatment Guidelines, above).

The NCEP classification of cholesterol levels in pediatric patients with a familial history of either hypercholesterolemia or premature cardiovascular disease is summarized in Table 7.

TABLE 7
NCEP Classification of Cholesterol Levels in Pediatric Patients with a Familial History of Either HeFH or Premature CVD

Category	Total-C (mg/dL)	LDL-C (mg/dL)
Acceptable	<170	<110
Borderline	170-199	110-129
High	≥200	≥130

Since the goal of treatment is to lower LDL-C, the NCEP recommends that LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available, should the total-C be used to monitor therapy.

ZOCOR is indicated to reduce elevated LDL-C and TG levels in patients with Type IIb hyperlipidemia (where hypercholesterolemia is the major abnormality). However, it has not been studied in conditions where the major abnormality is elevation of chylomicrons (i.e., hyperlipidemia Fredrickson types I and V).[4]

[4]Classification of Hyperlipoproteinemias

Type	Lipoproteins elevated	Lipid Elevations major	Lipid Elevations minor
I (rare)	chylomicrons	TG	↑→C
IIa	LDL	C	—
IIb	LDL, VLDL	C	TG
III (rare)	IDL	C/TG	—
IV	VLDL	TG	↑→C
V (rare)	chylomicrons, VLDL	TG	↑→C

C = cholesterol, TG = triglycerides,
LDL = low-density lipoprotein,
VLDL = very-low-density lipoprotein,
IDL = intermediate-density lipoprotein.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases (see WARNINGS).

Pregnancy and lactation. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development,

Continued on next page

Zocor—Cont.

including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as ZOCOR to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, ZOCOR is contraindicated during pregnancy and in nursing mothers. **ZOCOR should be administered to women of childbearing age only when such patients are highly unlikely to conceive.** If the patient becomes pregnant while taking this drug, ZOCOR should be discontinued immediately and the patient should be apprised of the potential hazard to the fetus (see PRECAUTIONS, *Pregnancy*).

WARNINGS

Myopathy/Rhabdomyolysis

Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above 10× the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma.

- **The risk of myopathy/rhabdomyolysis is increased by concomitant use of simvastatin with the following:**

  Potent inhibitors of CYP3A4: Cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily), particularly with higher doses of simvastatin (see below; CLINICAL PHARMACOLOGY, *Pharmacokinetics*; PRECAUTIONS, *Drug Interactions*, *CYP3A4 Interactions*).

  Other drugs:

  Gemfibrozil particularly with higher doses of simvastatin (see below; PRECAUTIONS, *Drug Interactions*, *Interactions with lipid-lowering drugs that can cause myopathy when given alone*; DOSAGE AND ADMINISTRATION).

  Other lipid-lowering drugs (other fibrates or ≥1 g/day of niacin) that can cause myopathy when given alone (see below; PRECAUTIONS, *Drug Interactions*, *Interactions with lipid-lowering drugs that can cause myopathy when given alone*).

  Danazol particularly with higher doses of simvastatin (see below; PRECAUTIONS, *Drug Interactions*, *Other drug interactions*).

  Amiodarone or verapamil with higher doses of simvastatin (see below; PRECAUTIONS, *Drug Interactions*, *Other drug interactions*). In an ongoing clinical trial, myopathy has been reported in 6% of patients receiving simvastatin 80 mg and amiodarone. In an analysis of clinical trials involving 25,248 patients treated with simvastatin 20 to 80 mg, the incidence of myopathy was higher in patients receiving verapamil and simvastatin (4/635; 0.63%) than in patients taking simvastatin without a calcium channel blocker (13/21,224; 0.061%).
- **The risk of myopathy/rhabdomyolysis is dose related.** The incidence in clinical trials, in which patients were carefully monitored and some interacting drugs were excluded, has been approximately 0.02% at 20 mg, 0.07% at 40 mg and 0.3% at 80 mg.

Consequently:

1. Use of simvastatin concomitantly with itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily) should be avoided. If treatment with itraconazole, ketoconazole, erythromycin, clarithromycin, or telithromycin is unavoidable, therapy with simvastatin should be suspended during the course of treatment. Concomitant use with other medicines labeled as having a potent inhibitory effect on CYP3A4 at therapeutic doses should be avoided unless the benefits of combined therapy outweigh the increased risk.

2. The dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with gemfibrozil. The combined use of simvastatin with gemfibrozil should be avoided, unless the benefits are likely to outweigh the increased risks of this drug combination. Caution should be used when prescribing other lipid-lowering drugs (other fibrates or lipid-lowering doses (≥1 g/day) of niacin) with simvastatin, as these agents can cause myopathy when given alone. **The benefit of further alterations in lipid levels by the combined use of simvastatin with fibrates or niacin should be carefully weighed against the potential risks of these combinations.** Addition of fibrates or niacin to simvastatin typically provides little additional reduction in LDL-C, but further reductions of TG and further increases in HDL-C may be obtained.

3. The dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with cyclosporine or danazol. The benefits of the use of simvastatin in patients receiving cyclosporine or danazol should be carefully weighed against the risks of these combinations.

4. The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone or verapamil. The combined use of simvastatin at doses higher than 20 mg daily with amiodarone or verapamil should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy.

5. All patients starting therapy with simvastatin, or whose dose of simvastatin is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. Simvastatin therapy should be discontinued immediately if myopathy is diagnosed or suspected. The presence of these symptoms, and/or a CK level >10 times the ULN indicates myopathy. In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CK increases resolved. Periodic CK determinations may be considered in patients starting therapy with simvastatin or whose dose is being increased, but there is no assurance that such monitoring will prevent myopathy.

6. Many of the patients who have developed rhabdomyolysis on therapy with simvastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients merit closer monitoring. Therapy with simvastatin should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

Liver Dysfunction

Persistent increases (to more than 3× the ULN) in serum transaminases have occurred in approximately 1% of patients who received simvastatin in clinical studies. When drug treatment was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity.

In 4S (see CLINICAL PHARMACOLOGY, *Clinical Studies*), the number of patients with more than one transaminase elevation to > 3× ULN, over the course of the study, was not significantly different between the simvastatin and placebo groups (14 [0.7%] vs. 12 [0.6%]). Elevated transaminases resulted in the discontinuation of 8 patients from therapy in the simvastatin group (n=2,221) and 5 in the placebo group (n=2,223). Of the 1,986 simvastatin treated patients in 4S with normal liver function tests (LFTs) at baseline, only 8 (0.4%) developed consecutive LFT elevations to > 3× ULN and/or were discontinued due to transaminase elevations during the 5.4 years (median follow-up) of the study. Among these 8 patients, 5 initially developed these abnormalities within the first year. All of the patients in this study received a starting dose of 20 mg of simvastatin; 37% were titrated to 40 mg.

In 2 controlled clinical studies in 1,105 patients, the 12-month incidence of persistent hepatic transaminase elevation without regard to drug relationship was 0.9% and 2.1% at the 40- and 80-mg dose, respectively. No patients developed persistent liver function abnormalities following the initial 6 months of treatment at a given dose.

It is recommended that liver function tests be performed before the initiation of treatment, and thereafter when clinically indicated. Patients titrated to the 80-mg dose should receive an additional test prior to titration, 3 months after titration to the 80-mg dose, and periodically thereafter (e.g., semiannually) for the first year of treatment. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of 3× ULN or greater persist, withdrawal of therapy with ZOCOR is recommended.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of simvastatin.

As with other lipid-lowering agents, moderate (less than 3× ULN) elevations of serum transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms and did not require interruption of treatment.

PRECAUTIONS

General

Simvastatin may cause elevation of CK and transaminase levels (see WARNINGS and ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with simvastatin.

Information for Patients

Patients should be advised about substances they should not take concomitantly with simvastatin and be advised to report promptly unexplained muscle pain, tenderness, or weakness (see list below and WARNINGS, *Myopathy/Rhabdomyolysis*). Patients should also be advised to inform other physicians prescribing a new medication that they are taking ZOCOR.

Drug Interactions

CYP3A4 Interactions

Simvastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. Potent inhibitors of CYP3A4 (below) increase the risk of myopathy by reducing the elimination of simvastatin.

See WARNINGS, *Myopathy/Rhabdomyolysis*, and CLINICAL PHARMACOLOGY, *Pharmacokinetics*.

Itraconazole
Ketoconazole
Erythromycin
Clarithromycin
Telithromycin
HIV protease inhibitors
Nefazodone
Cyclosporine
Large quantities of grapefruit juice (>1 quart daily)

Interactions with lipid-lowering drugs that can cause myopathy when given alone

See WARNINGS, *Myopathy/Rhabdomyolysis*.

The risk of myopathy is increased by gemfibrozil (see DOSAGE AND ADMINISTRATION) and to a lesser extent by other fibrates and niacin (nicotinic acid) (≥1 g/day).

Other drug interactions

Danazol: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of danazol particularly with higher doses of simvastatin (see WARNINGS, *Myopathy/Rhabdomyolysis*).

Amiodarone or Verapamil: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone or verapamil with higher doses of simvastatin (see WARNINGS, *Myopathy/Rhabdomyolysis*).

Propranolol: In healthy male volunteers there was a significant decrease in mean C_{max}, but no change in AUC, for simvastatin total and active inhibitors with concomitant administration of single doses of ZOCOR and propranolol. The clinical relevance of this finding is unclear. The pharmacokinetics of the enantiomers of propranolol were not affected.

Digoxin: Concomitant administration of a single dose of digoxin in healthy male volunteers receiving simvastatin resulted in a slight elevation (less than 0.3 ng/mL) in digoxin concentrations in plasma (as measured by a radioimmunoassay) compared to concomitant administration of placebo and digoxin. Patients taking digoxin should be monitored appropriately when simvastatin is initiated.

Warfarin: In two clinical studies, one in normal volunteers and the other in hypercholesterolemic patients, simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratio (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in the volunteer and patient studies, respectively. With other reductase inhibitors, clinically evident bleeding and/or increased prothrombin time has been reported in a few patients taking coumarin anticoagulants concomitantly. In such patients, prothrombin time should be determined before starting simvastatin and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of simvastatin is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

CNS Toxicity

Optic nerve degeneration was seen in clinically normal dogs treated with simvastatin for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 12 times higher than the mean plasma drug level in humans taking 80 mg/day.

A chemically similar drug in this class also produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean plasma drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits and necrosis of small vessels were seen in dogs treated with simvastatin at a dose of 360 mg/kg/day, a dose that produced mean plasma drug levels that were about 14 times higher than the mean plasma drug levels in humans taking 80 mg/day. Similar CNS vascular lesions have been observed with several other drugs of this class.

There were cataracts in female rats after two years of treatment with 50 and 100 mg/kg/day (22 and 25 times the human AUC at 80 mg/day, respectively) and in dogs after three months at 90 mg/kg/day (19 times) and at two years at 50 mg/kg/day (5 times).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 72-week carcinogenicity study, mice were administered daily doses of simvastatin of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately 1, 4, and 8 times higher than the mean human plasma drug level, respectively (as total inhibitory activity based on AUC) after an 80-mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls. No evidence of a tumorigenic effect was observed at 25 mg/kg/day.

In a separate 92-week carcinogenicity study in mice at doses up to 25 mg/kg/day, no evidence of a tumorigenic effect was

observed (mean plasma drug levels were 1 times higher than humans given 80 mg simvastatin as measured by AUC).

In a two-year study in rats at 25 mg/kg/day, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 11 times higher levels of simvastatin than in humans given 80 mg simvastatin (as measured by AUC).

A second two-year rat carcinogenicity study with doses of 50 and 100 mg/kg/day produced hepatocellular adenomas and carcinomas (in female rats at both doses and in males at 100 mg/kg/day). Thyroid follicular cell adenomas were increased in males and females at both doses; thyroid follicular cell carcinomas were increased in females at 100 mg/kg/day. The increased incidence of thyroid neoplasms appears to be consistent with findings from other HMG-CoA reductase inhibitors. These treatment levels represented plasma drug levels (AUC) of approximately 7 and 15 times (males) and 22 and 25 times (females) the mean human plasma drug exposure after an 80 milligram daily dose.

No evidence of mutagenicity was observed in a microbial mutagenicity (Ames) test with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (4 times the maximum human exposure level, based on AUC, in patients receiving 80 mg/day); however, this effect was not observed during a subsequent fertility study in which simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal maturation). No microscopic changes were observed in the testes of rats from either study. At 180 mg/kg/day, (which produces exposure levels 22 times higher than those in humans taking 80 mg/day based on surface area, mg/m^2), seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation at 10 mg/kg/day, (approximately 2 times the human exposure, based on AUC, at 80 mg/day). The clinical significance of these findings is unclear.

Pregnancy

Pregnancy Category X

See CONTRAINDICATIONS.

Safety in pregnant women has not been established.

Simvastatin was not teratogenic in rats at doses of 25 mg/kg/day or in rabbits at doses up to 10 mg/kg daily. These doses resulted in 3 times (rat) or 3 times (rabbit) the human exposure based on mg/m^2 surface area. However, in studies with another structurally-related HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice.

Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. In a review[5] of approximately 100 prospectively followed pregnancies in women exposed to ZOCOR or another structurally related HMG-CoA reductase inhibitor, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a 3- to 4-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. As safety in pregnant women has not been established and there is no apparent benefit to therapy with ZOCOR during pregnancy (see CONTRAINDICATIONS), treatment should be immediately discontinued as soon as pregnancy is recognized. ZOCOR should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards.

[5] Manson, J.M., Freyssinges, C., Ducrocq, M.B., Stephenson, W.P., Postmarketing Surveillance of Lovastatin and Simvastatin Exposure During Pregnancy, *Reproductive Toxicology*, 10(6):439-446, 1996.

Nursing Mothers

It is not known whether simvastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women taking simvastatin should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use

Safety and effectiveness of simvastatin in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial in adolescent boys and in girls who were at least 1 year postmenarche. Patients treated with simvastatin had an adverse experience profile generally similar to that of patients treated with placebo. **Doses greater than 40 mg have not been studied in this population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. See CLINICAL PHARMACOLOGY, *Clinical Studies in Adolescents;* ADVERSE REACTIONS, *Adolescent Patients;* and DOSAGE AND ADMINISTRATION, *Adolescents (10-17 years of age) with Heterozygous Familial Hypercholesterolemia.* Adolescent females should be counseled on appropriate contraceptive methods while on simvastatin therapy (see CONTRAINDICATIONS and PRECAUTIONS, *Pregnancy*). Simvastatin has not been studied in patients younger than 10 years of age, nor in pre-menarchal girls.

Geriatric Use

A pharmacokinetic study with simvastatin showed the mean plasma level of HMG-CoA reductase inhibitory activity to be approximately 45% higher in elderly patients between 70-78 years of age compared with patients between 18-30 years of age. In 4S, 1,021 (23%) of 4,444 patients were 65 or older. In 4S, lipid-lowering efficacy was at least as great in elderly patients compared with younger patients. In this study, ZOCOR significantly reduced total mortality and CHD mortality in elderly patients with a history of CHD. In HPS, 52% of patients were elderly (4,891 patients 65-69 years and 5,806 patients 70 years or older). The relative risk reductions of CHD death, non-fatal MI, coronary and non-coronary revascularization procedures, and stroke were similar in older and younger patients (see CLINICAL PHARMACOLOGY). In HPS, among 32,145 patients entering the active run-in period, there were 2 cases of myopathy/rhabdomyolysis; these patients were aged 67 and 73. Of the 7 cases of myopathy/rhabdomyolysis among 10,269 patients allocated to simvastatin, 4 were aged 65 or more (at baseline), of whom one was over 75. There were no overall differences in safety between older and younger patients in either 4S or HPS.

ADVERSE REACTIONS

In the pre-marketing controlled clinical studies and their open extensions (2,423 patients with mean duration of follow-up of approximately 18 months), 1.4% of patients were discontinued due to adverse experiences attributable to ZOCOR. Adverse reactions have usually been mild and transient. ZOCOR has been evaluated for serious adverse reactions in more than 21,000 patients and is generally well tolerated.

Clinical Adverse Experiences

In Adults

Adverse experiences occurring in adults at an incidence of 1% or greater in patients treated with ZOCOR, regardless of causality, in controlled clinical studies are shown in Table 8. [See table 8 above]

Scandinavian Simvastatin Survival Study

Clinical Adverse Experiences

In 4S (see CLINICAL PHARMACOLOGY, *Clinical Studies*) involving 4,444 patients treated with 20-40 mg/day of ZOCOR (n=2,221) or placebo (n=2,223), the safety and tolerability profiles were comparable between groups over the median 5.4 years of the study. The clinical adverse experiences reported as possibly, probably, or definitely drug-related in ≥ 0.5% in either treatment group are shown in Table 9.

TABLE 9
Drug-Related Clinical Adverse Experiences in 4S
Incidence 0.5 Percent or Greater

	ZOCOR (N = 2,221) %	Placebo (N = 2,223) %
Body as a Whole		
Abdominal pain	0.9	0.9
Gastrointestinal		
Diarrhea	0.5	0.3
Dyspepsia	0.6	0.5
Flatulence	0.9	0.7
Nausea	0.4	0.6
Musculoskeletal		
Myalgia	1.2	1.3
Skin		
Eczema	0.8	0.8
Pruritus	0.5	0.4
Rash	0.6	0.6
Special Senses		
Cataract	0.5	0.8

Heart Protection Study

Clinical Adverse Experiences

In HPS (see CLINICAL PHARMACOLOGY, *Clinical Studies*), involving 20,536 patients treated with ZOCOR 40 mg/day (n=10,269) or placebo (n=10,267), the safety profiles were comparable between patients treated with ZOCOR and patients treated with placebo over the mean 5 years of the study. In this large trial, only serious adverse events and discontinuations due to any adverse events were recorded. Discontinuation rates due to adverse experiences were comparable (4.8% in patients treated with ZOCOR compared with 5.1% in patients treated with placebo). The incidence of myopathy/rhabdomyolysis was <0.1% in patients treated with ZOCOR.

The following effects have been reported with drugs in this class. Not all the effects listed below have necessarily been associated with simvastatin therapy.

Skeletal: muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgias.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances, anxiety, insomnia, depression.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Skin: alopecia, pruritus. A variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails) have been reported.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, γ-glutamyl transpeptidase, and bilirubin; thyroid function abnormalities.

Laboratory Tests

Marked persistent increases of serum transaminases have been noted (see WARNINGS, *Liver Dysfunction*). About 5% of patients had elevations of CK levels of 3 or more times the normal value on one or more occasions. This was attributable to the noncardiac fraction of CK. Muscle pain or dysfunction usually was not reported (see WARNINGS, *Myopathy/Rhabdomyolysis*).

Concomitant Lipid-Lowering Therapy

In controlled clinical studies in which simvastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with simvastatin or cholestyramine. The combined use of simvastatin at doses exceeding 10 mg/day with gemfibrozil should be avoided (see WARNINGS, *Myopathy/Rhabdomyolysis*).

Adolescent Patients (ages 10-17 years)

In a 48-week, controlled study in adolescent boys and girls who were at least 1 year post-menarche, 10-17 years of age with heterozygous familial hypercholesterolemia (n=175), the safety and tolerability profile of the group treated with ZOCOR (10-40 mg daily) was generally similar to that of the group treated with placebo, with the most common adverse experiences observed in both groups being upper respiratory infection, headache, abdominal pain, and nausea (see CLINICAL PHARMACOLOGY, *Clinical Studies in Adolescents*, and PRECAUTIONS, *Pediatric Use*).

TABLE 8
Adverse Experiences in Clinical Studies Incidence 1 Percent or Greater, Regardless of Causality

	ZOCOR (N = 1,583) %	Placebo (N = 157) %	Cholestyramine (N = 179) %
Body as a Whole			
Abdominal pain	3.2	3.2	8.9
Asthenia	1.6	2.5	1.1
Gastrointestinal			
Constipation	2.3	1.3	29.1
Diarrhea	1.9	2.5	7.8
Dyspepsia	1.1	—	4.5
Flatulence	1.9	1.3	14.5
Nausea	1.3	1.9	10.1
Nervous System/Psychiatric			
Headache	3.5	5.1	4.5
Respiratory			
Upper respiratory infection	2.1	1.9	3.4

Continued on next page

Zocor—Cont.

OVERDOSAGE

Significant lethality was observed in mice after a single oral dose of 9 g/m^2. No evidence of lethality was observed in rats or dogs treated with doses of 30 and 100 g/m^2, respectively. No specific diagnostic signs were observed in rodents. At these doses the only signs seen in dogs were emesis and mucoid stools.

A few cases of overdosage with ZOCOR have been reported; the maximum dose taken was 3.6 g. All patients recovered without sequelae. Until further experience is obtained, no specific treatment of overdosage with ZOCOR can be recommended.

The dialyzability of simvastatin and its metabolites in man is not known at present.

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet. In patients with CHD or at high risk of CHD, ZOCOR can be started simultaneously with diet. The dosage should be individualized according to the goals of therapy and the patient's response. (For the treatment of adult dyslipidemia, see NCEP Treatment Guidelines. For the reduction in risks of major coronary events, see CLINICAL PHARMACOLOGY, *Clinical Studies in Adults*.) The dosage range is 5-80 mg/day (see below).

The recommended usual starting dose is 20 to 40 mg once a day in the evening. For patients at high risk for a CHD event due to existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, the recommended starting dose is 40 mg/day. Lipid determinations should be performed after 4 weeks of therapy and periodically thereafter. See below for dosage recommendations in special populations (i.e., homozygous familial hypercholesterolemia, adolescents and renal insufficiency) or for patients receiving concomitant therapy (i.e., cyclosporine, danazol, amiodarone, verapamil, or gemfibrozil).

Patients with Homozygous Familial Hypercholesterolemia

The recommended dosage for patients with homozygous familial hypercholesterolemia is ZOCOR 40 mg/day in the evening or 80 mg/day in 3 divided doses of 20 mg, 20 mg, and an evening dose of 40 mg. ZOCOR should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

Adolescents (10-17 years of age) with Heterozygous Familial Hypercholesterolemia

The recommended usual starting dose is 10 mg once a day in the evening. The recommended dosing range is 10-40 mg/day; the maximum recommended dose is 40 mg/day. Doses should be individualized according to the recommended goal of therapy (see NCEP Pediatric Panel Guidelines[6] and CLINICAL PHARMACOLOGY). Adjustments should be made at intervals of 4 weeks or more.

Concomitant Lipid-Lowering Therapy

ZOCOR is effective alone or when used concomitantly with bile-acid sequestrants. If ZOCOR is used in combination with gemfibrozil, the dose of ZOCOR should not exceed 10 mg/day (see WARNINGS, *Myopathy/Rhabdomyolysis* and PRECAUTIONS, *Drug Interactions*).

Patients taking Cyclosporine or Danazol

In patients taking cyclosporine or danazol concomitantly with ZOCOR (see WARNINGS, *Myopathy/Rhabdomyolysis*), therapy should begin with 5 mg/day and should not exceed 10 mg/day.

Patients taking Amiodarone or Verapamil

In patients taking amiodarone or verapamil concomitantly with ZOCOR, the dose should not exceed 20 mg/day (see WARNINGS, *Myopathy/Rhabdomyolysis* and PRECAUTIONS, *Drug Interactions, Other drug interactions*).

Patients with Renal Insufficiency

Because ZOCOR does not undergo significant renal excretion, modification of dosage should not be necessary in patients with mild to moderate renal insufficiency. However, caution should be exercised when ZOCOR is administered to patients with severe renal insufficiency; such patients should be started at 5 mg/day and be closely monitored (see CLINICAL PHARMACOLOGY, *Pharmacokinetics* and WARNINGS, *Myopathy/Rhabdomyolysis*).

[6] National Cholesterol Education Program (NCEP): Highlights of the Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics*. 89(3): 495-501. 1992.

HOW SUPPLIED

No. 3588 — Tablets ZOCOR 5 mg are buff, shield-shaped, film-coated tablets, coded MSD 726 on one side and ZOCOR on the other. They are supplied as follows:
NDC 0006-0726-31 unit of use bottles of 30
NDC 0006-0726-61 unit of use bottles of 60
NDC 0006-0726-54 unit of use bottles of 90
NDC 0006-0726-28 unit dose packages of 100
NDC 0006-0726-82 bottles of 1000.

No. 3589 — Tablets ZOCOR 10 mg are peach, shield-shaped, film-coated tablets, coded MSD 735 on one side and ZOCOR on the other. They are supplied as follows:
NDC 0006-0735-31 unit of use bottles of 30
NDC 0006-0735-54 unit of use bottles of 90
NDC 0006-0735-28 unit dose packages of 100
NDC 0006-0735-82 bottles of 1000
NDC 0006-0735-87 bottles of 10,000.

No. 3590 — Tablets ZOCOR 20 mg are tan, shield-shaped, film-coated tablets, coded MSD 740 on one side and ZOCOR on the other. They are supplied as follows:
NDC 0006-0740-31 unit of use bottles of 30
NDC 0006-0740-61 unit of use bottles of 60
NDC 0006-0740-54 unit of use bottles of 90
NDC 0006-0740-28 unit dose packages of 100
NDC 0006-0740-82 bottles of 1000
NDC 0006-0740-87 bottles of 10,000.

No. 3591 — Tablets ZOCOR 40 mg are brick red, shield-shaped, film-coated tablets, coded MSD 749 on one side and ZOCOR on the other. They are supplied as follows:
NDC 0006-0749-31 unit of use bottles of 30
NDC 0006-0749-61 unit of use bottles of 60
NDC 0006-0749-54 unit of use bottles of 90
NDC 0006-0749-28 unit dose packages of 100
NDC 0006-0749-82 bottles of 1000.

No. 6577 — Tablets ZOCOR 80 mg are brick red, capsule-shaped, film-coated tablets, coded 543 on one side and 80 on the other. They are supplied as follows:
NDC 0006-0543-31 unit of use bottles of 30
NDC 0006-0543-61 unit of use bottles of 60
NDC 0006-0543-54 unit of use bottles of 90
NDC 0006-0543-28 unit dose packages of 100
NDC 0006-0543-82 bottles of 1000.

Storage

Store between 5-30°C (41-86°F).

Tablets ZOCOR (simvastatin) 5 mg, 10 mg, 20 mg, and 40 mg are manufactured by:
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA
Tablets ZOCOR (simvastatin) 80 mg are manufactured for:
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA
By:
MERCK SHARP & DOHME LTD,
Cramlington, Northumberland, UK NE23 3JU
9556648, Issued November 2004

Shown in Product Identification Guide, page 323

Merck/Schering-Plough Pharmaceuticals
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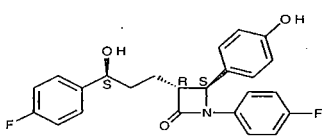
VYTORIN™ 10/10 ℞
(EZETIMIBE 10 MG/SIMVASTATIN 10 MG TABLETS)
VYTORIN™ 10/20 ℞
(EZETIMIBE 10 MG/SIMVASTATIN 20 MG TABLETS)
VYTORIN™ 10/40 ℞
(EZETIMIBE 10 MG/SIMVASTATIN 40 MG TABLETS)
VYTORIN™ 10/80 ℞
(EZETIMIBE 10 MG/SIMVASTATIN 80 MG TABLETS)
[*vī-tōr-in*]

DESCRIPTION

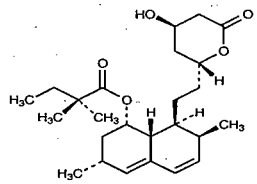
VYTORIN contains ezetimibe, a selective inhibitor of intestinal cholesterol and related phytosterol absorption, and simvastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor.

The chemical name of ezetimibe is 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]- 4(S)-(4-hydroxyphenyl)-2-azetidinone. The empirical formula is $C_{24}H_{21}F_2NO_3$ and its molecular weight is 409.4.

Ezetimibe is a white, crystalline powder that is freely to very soluble in ethanol, methanol, and acetone and practically insoluble in water. Its structural formula is:



Simvastatin, an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form, which is an inhibitor of HMG-CoA reductase. Simvastatin is butanoic acid, 2,2-dimethyl, 1,2,3,7,8,8a-hexahydro-3,7- dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1*S*- [1α,3α,7β,8β(2*S**,4*S**),-8aβ]]. The empirical formula of simvastatin is $C_{25}H_{38}O_5$ and its molecular weight is 418.57. Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol and ethanol. Its structural formula is:



VYTORIN is available for oral use as tablets containing 10 mg of ezetimibe, and 10 mg of simvastatin (VYTORIN 10/10), 20 mg of simvastatin (VYTORIN 10/20), 40 mg of simvastatin (VYTORIN 10/40), or 80 mg of simvastatin (VYTORIN 10/80). Each tablet contains the following inactive ingredients: butylated hydroxyanisole NF, citric acid monohydrate USP, croscarmellose sodium NF, hydroxypropyl methylcellulose USP, lactose monohydrate NF, magnesium stearate NF, microcrystalline cellulose NF, and propyl gallate NF.

CLINICAL PHARMACOLOGY

Background

Clinical studies have demonstrated that elevated levels of total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C) and apolipoprotein B (Apo B), the major protein constituent of LDL, promote human atherosclerosis. In addition, decreased levels of high-density lipoprotein cholesterol (HDL-C) are associated with the development of atherosclerosis. Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis. The independent effect of raising HDL-C or lowering triglycerides (TG) on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

Mode of Action

VYTORIN

Plasma cholesterol is derived from intestinal absorption and endogenous synthesis. VYTORIN contains ezetimibe and simvastatin, two lipid-lowering compounds with complementary mechanisms of action. VYTORIN reduces elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and increases HDL-C through dual inhibition of cholesterol absorption and synthesis.

Ezetimibe

Ezetimibe reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine. In a 2-week clinical study in 18 hypercholesterolemic patients, ezetimibe inhibited intestinal cholesterol absorption by 54%, compared with placebo. Ezetimibe had no clinically meaningful effect on the plasma concentrations of the fat-soluble vitamins A, D, and E and did not impair adrenocortical steroid hormone production.

Ezetimibe localizes and appears to act at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood; this distinct mechanism is complementary to that of HMG-CoA reductase inhibitors (see CLINICAL STUDIES).

Simvastatin

Simvastatin reduces cholesterol by inhibiting the conversion of HMG-CoA to mevalonate, an early step in the biosynthetic pathway for cholesterol. In addition, simvastatin reduces VLDL and TG and increases HDL-C.

Pharmacokinetics

Absorption

VYTORIN

VYTORIN is bioequivalent to coadministered ezetimibe and simvastatin.

Ezetimibe

After oral administration, ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide).

Effect of Food on Oral Absorption

Ezetimibe

Concomitant food administration (high-fat or non-fat meals) had no effect on the extent of absorption of ezetimibe when administered as 10-mg tablets. The C_{max} value of ezetimibe was increased by 38% with consumption of high-fat meals.

Simvastatin

Relative to the fasting state, the plasma profiles of both active and total inhibitors of HMG-CoA reductase were not affected when simvastatin was administered immediately before an American Heart Association recommended low-fat meal.

Distribution

Ezetimibe

Ezetimibe and ezetimibe-glucuronide are highly bound (>90%) to human plasma proteins.

Simvastatin

Both simvastatin and its β-hydroxyacid metabolite are highly bound (approximately 95%) to human plasma proteins. When radiolabeled simvastatin was administered to rats, simvastatin-derived radioactivity crossed the blood-brain barrier.

Metabolism and Excretion

Ezetimibe

Ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation with subsequent biliary and renal excretion. Minimal oxidative metabolism has been observed in all species evaluated.

In humans, ezetimibe is rapidly metabolized to ezetimibe-glucuronide. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10 to 20% and 80 to 90% of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with a half-life of approximately 22 hours for both ezetimibe and ezetimibe-glucuronide. Plasma concentration-time profiles exhibit multiple peaks, suggesting enterohepatic recycling.

Following oral administration of ^{14}C-ezetimibe (20 mg) to human subjects, total ezetimibe (ezetimibe + ezetimibe-glucuronide) accounted for approximately 93% of the total radioactivity in plasma. After 48 hours, there were no detectable levels of radioactivity in the plasma.

Approximately 78% and 11% of the administered radioactivity were recovered in the feces and urine, respectively, over a 10-day collection period. Ezetimibe was the major component in feces and accounted for 69% of the administered dose, while ezetimibe-glucuronide was the major component in urine and accounted for 9% of the administered dose.

Simvastatin

Simvastatin is a lactone that is readily hydrolyzed *in vivo* to the corresponding β-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Inhibition of HMG-CoA reductase is a basis for an assay in pharmacokinetic studies of the β-hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors) in plasma following administration of simvastatin. The major active metabolites of simvastatin present in human plasma are the β-hydroxyacid of simvastatin and its 6′- hydroxy, 6′-hydroxymethyl, and 6′-exomethylene derivatives.

Plasma concentrations of total radioactivity (simvastatin plus ^{14}C-metabolites) peaked at 4 hours and declined rapidly to about 10% of peak by 12 hours postdose. Simvastatin undergoes extensive first-pass extraction in the liver, its primary site of action, with subsequent excretion of drug equivalents in the bile. As a consequence of extensive hepatic extraction of simvastatin (estimated to be >60% in man), the availability of drug to the general circulation is low.

Following an oral dose of ^{14}C-labeled simvastatin in man, 13% of the dose was excreted in urine and 60% in feces. The latter represents absorbed drug equivalents excreted in bile, as well as any unabsorbed drug.

In a single-dose study in nine healthy subjects, it was estimated that less than 5% of an oral dose of simvastatin reaches the general circulation as active inhibitors.

Special Populations

Geriatric Patients

Ezetimibe

In a multiple-dose study with ezetimibe given 10 mg once daily for 10 days, plasma concentrations for total ezetimibe were about 2-fold higher in older (≥65 years) healthy subjects compared to younger subjects.

Simvastatin

In a study including 16 elderly patients between 70 and 78 years of age who received simvastatin 40 mg/day, the mean plasma level of HMG-CoA reductase inhibitory activity was increased approximately 45% compared with 18 patients between 18–30 years of age.

Pediatric Patients

Ezetimibe

In a multiple-dose study with ezetimibe given 10 mg once daily for 7 days, the absorption and metabolism of ezetimibe were similar in adolescents (10 to 18 years) and adults. Based on total ezetimibe, there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the pediatric population <10 years of age are not available.

Gender

Ezetimibe

In a multiple-dose study with ezetimibe given 10 mg once daily for 10 days, plasma concentrations for total ezetimibe were slightly higher (<20%) in women than in men.

Race

Ezetimibe

Based on a meta-analysis of multiple-dose pharmacokinetic studies, there were no pharmacokinetic differences between Blacks and Caucasians. There were too few patients in other racial or ethnic groups to permit further pharmacokinetic comparisons.

Hepatic Insufficiency

Ezetimibe

After a single 10-mg dose of ezetimibe, the mean exposure (based on area under the curve [AUC]) to total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic insufficiency (Child-Pugh score 5 to 6), compared to healthy subjects. The mean AUC values for total ezetimibe and ezetimibe increased approximately 3- to 4-fold and 5- to 6-fold, respectively, in patients with moderate (Child-Pugh score 7 to 9) or severe hepatic impairment (Child-Pugh score 10 to 15). In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic insufficiency, the mean AUC for total ezetimibe and ezetimibe increased approximately 4-fold compared to healthy subjects.

Renal Insufficiency

Ezetimibe

After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl ≤30 mL/min/1.73 m^2), the mean AUC for total ezetimibe and ezetimibe increased approximately 1.5-fold, compared to healthy subjects (n=9).

Simvastatin

Pharmacokinetic studies with another statin having a similar principal route of elimination to that of simvastatin have suggested that for a given dose level higher systemic exposure may be achieved in patients with severe renal insufficiency (as measured by creatinine clearance).

Drug Interactions **(See also PRECAUTIONS, *Drug Interactions*)**

No clinically significant pharmacokinetic interaction was seen when ezetimibe was coadministered with simvastatin. Specific pharmacokinetic drug interaction studies with VYTORIN have not been performed.

Cytochrome P450: Ezetimibe had no significant effect on a series of probe drugs (caffeine, dextromethorphan, tolbutamide, and IV midazolam) known to be metabolized by cytochrome P450 (1A2, 2D6, 2C8/9 and 3A4) in a "cocktail" study of twelve healthy adult males. This indicates that ezetimibe is neither an inhibitor nor an inducer of these cytochrome P450 isozymes, and it is unlikely that ezetimibe will affect the metabolism of drugs that are metabolized by these enzymes.

In a study of 12 healthy volunteers, simvastatin at the 80-mg dose had no effect on the metabolism of the probe cytochrome P450 isoform 3A4 (CYP3A4) substrates midazolam and erythromycin. This indicates that simvastatin is not an inhibitor of CYP3A4, and, therefore, is not expected to affect the plasma levels of other drugs metabolized by CYP3A4.

Simvastatin is a substrate for CYP3A4. Potent inhibitors of CYP3A4 can raise the plasma levels of HMG-CoA reductase inhibitory activity and increase the risk of myopathy. (See WARNINGS, *Myopathy/Rhabdomyolysis* and PRECAUTIONS, *Drug Interactions*.)

Antacids: In a study of twelve healthy adults, a single dose of antacid (Supralox™ 20 mL) administration had no significant effect on the oral bioavailability of total ezetimibe, ezetimibe-glucuronide, or ezetimibe based on AUC values. The C_{max} value of total ezetimibe was decreased by 30%.

Cholestyramine: In a study of forty healthy hypercholesterolemic (LDL-C ≥130 mg/dL) adult subjects, concomitant cholestyramine (4 g twice daily) administration decreased the mean AUC of total ezetimibe and ezetimibe approximately 55% and 80%, respectively.

Cyclosporine: In a study of eight post-renal transplant patients with mildly impaired or normal renal function (creatinine clearance of >50 mL/min), stable doses of cyclosporine (75 to 150 mg twice daily) increased the mean AUC and C_{max} values of total ezetimibe 3.4-fold (range 2.3- to 7.9-fold) and 3.9-fold (range 3.0- to 4.4-fold), respectively, compared to a historical healthy control population (n=17). In a different study, a renal transplant patient with severe renal insufficiency (creatinine clearance of 13.2 mL/min/1.73 m^2) who was receiving multiple medications, including cyclosporine, demonstrated a 12-fold greater exposure to total ezetimibe compared to healthy subjects. In a two-period crossover study in twelve healthy subjects, daily administration of 20 mg ezetimibe for 8 days with a single 100-mg dose of cyclosporine on Day 7 resulted in a mean 15% increase in cyclosporine AUC (range 10% decrease to 51% increase) compared to a single 100-mg dose of cyclosporine alone (see PRECAUTIONS, *Drug Interactions*).

Fenofibrate: In a study of thirty-two healthy hypercholesterolemic (LDL-C ≥130 mg/dL) adult subjects, concomitant fenofibrate (200 mg once daily) administration increased the mean C_{max} and AUC values of total ezetimibe approximately 64% and 48%, respectively. Pharmacokinetics of fenofibrate were not significantly affected by ezetimibe (10 mg once daily).

Gemfibrozil: In a study of twelve healthy adult males, concomitant administration of gemfibrozil (600 mg twice daily) significantly increased the oral bioavailability of total ezetimibe by a factor of 1.7. Ezetimibe (10 mg once daily) did not significantly affect the bioavailability of gemfibrozil.

Grapefruit Juice: Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma concentrations of drugs metabolized by CYP3A4. In one study[1], 10 subjects consumed 200 mL of double-strength grapefruit juice (one can of frozen concentrate diluted with one rather than 3 cans of water) three times daily for 2 days and an additional 200 mL double-strength grapefruit juice together with, and 30 and 90 minutes following, a single dose of 60 mg simvastatin on the third day. This regimen of grapefruit juice resulted in mean increases in the concentration (as measured by the area under the concentration-time curve) of active and total HMG-CoA reductase inhibitory activity [measured using a radioenzyme inhibition assay both before (for active inhibitors) and after (for total inhibitors) base hydrolysis] of 2.4-fold and 3.6-fold, respectively, and of simvastatin and its β-hydroxyacid metabolite [measured using a chemical assay — liquid chromatography/tandem mass spectrometry] of 16-fold and 7-fold, respectively. In a second study, 16 subjects consumed one 8 oz glass of single-strength grapefruit juice (one can of frozen concentrate diluted with 3 cans of water) with breakfast for 3 consecutive days and a single dose of 20 mg simvastatin in the evening of the third day. This regimen of grapefruit juice resulted in a mean increase in the plasma concentration (as measured by the area under the concentration-time curve) of active and total HMG-CoA reductase inhibitory activity [using a validated enzyme inhibition assay different from that used in the first[1] study, both before (for active inhibitors) and after (for total inhibitors) base hydrolysis] of 1.13-fold and 1.18-fold, respectively, and of simvastatin and its β-hydroxyacid metabolite [measured using a chemical assay — liquid chromatography/tandem mass spectrometry] of 1.88-fold and 1.31-fold, respectively. The effect of amounts of grapefruit juice between those used in these two studies on simvastatin pharmacokinetics has not been studied.

[1] Lilja JJ, Kivisto KT, Neuvonen PJ. Clin Pharmacol Ther 1998;64(5):477-83.

ANIMAL PHARMACOLOGY

Ezetimibe

The hypocholesterolemic effect of ezetimibe was evaluated in cholesterol-fed Rhesus monkeys, dogs, rats, and mouse models of human cholesterol metabolism. Ezetimibe was found to have an ED_{50} value of 0.5 μg/kg/day for inhibiting the rise in plasma cholesterol levels in monkeys. The ED_{50} values in dogs, rats, and mice were 7, 30, and 700 μg/kg/day, respectively. These results are consistent with ezetimibe being a potent cholesterol absorption inhibitor.

In a rat model, where the glucuronide metabolite of ezetimibe (ezetimibe-glucuronide) was administered intraduodenally, the metabolite was as potent as ezetimibe in inhibiting the absorption of cholesterol, suggesting that the glucuronide metabolite had activity similar to the parent drug.

In 1-month studies in dogs given ezetimibe (0.03 to 300 mg/kg/day), the concentration of cholesterol in gallbladder bile increased ~2- to 4-fold. However, a dose of 300 mg/kg/day administered to dogs for one year did not result in gallstone formation or any other adverse hepatobiliary effects. In a 14-day study in mice given ezetimibe (0.3 to 5 mg/kg/day) and fed a low-fat or cholesterol-rich diet, the concentration of cholesterol in gallbladder bile was either unaffected or reduced to normal levels, respectively.

A series of acute preclinical studies was performed to determine the selectivity of ezetimibe for inhibiting cholesterol absorption. Ezetimibe inhibited the absorption of ^{14}C-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethyl estradiol, or the fat-soluble vitamins A and D.

In 4- to 12-week toxicity studies in mice, ezetimibe did not induce cytochrome P450 drug metabolizing enzymes. In toxicity studies, a pharmacokinetic interaction of ezetimibe with HMG-CoA reductase inhibitors (parents or their active hydroxy acid metabolites) was seen in rats, dogs, and rabbits.

CLINICAL STUDIES

Primary Hypercholesterolemia

VYTORIN

VYTORIN reduces total-C, LDL-C, Apo B, TG, and non-HDL-C, and increases HDL-C in patients with hypercholesterolemia. Maximal to near maximal response is generally achieved within 2 weeks and maintained during chronic therapy.

VYTORIN is effective in men and women with hypercholesterolemia. Experience in non-Caucasians is limited and does not permit a precise estimate of the magnitude of the effects of VYTORIN.

In a multicenter, double-blind, placebo-controlled, 12-week trial, 1528 hypercholesterolemic patients were randomized to one of ten treatment groups: placebo, ezetimibe (10 mg), simvastatin (10 mg, 20 mg, 40 mg, or 80 mg), or VYTORIN (10/10, 10/20, 10/40, or 10/80).

When patients receiving VYTORIN were compared to those receiving all doses of simvastatin, VYTORIN significantly lowered total-C, LDL-C, Apo B, TG, and non-HDL-C. The effects of VYTORIN on HDL-C were similar to the effects seen with simvastatin. Further analysis showed VYTORIN significantly increased HDL-C compared with placebo. (See Table 1.) The lipid response to VYTORIN was similar in patients with TG levels greater than or less than 200 mg/dL. [See table 1 at top of next page]

In a multicenter, double-blind, controlled, 23-week study, 710 patients with known CHD or CHD risk equivalents, as defined by the NCEP ATP III guidelines, and an LDL-C ≥130 mg/dL were randomized to one of four treatment groups: coadministered ezetimibe and simvastatin equivalent to VYTORIN (10/10, 10/20, and 10/40), or simvastatin 20 mg. Patients not reaching an LDL-C <100 mg/dL had their simvastatin dose titrated at 6-week intervals to a maximal dose of 80 mg.

At Week 5, the LDL-C reductions with VYTORIN 10/10, 10/20, or 10/40 were significantly larger than with simvastatin 20 mg (see Table 2).

Continued on next page